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THE AMERICAN JOURNAL
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DECEMBER, 1945

ORIGINAL ARTICLES

CONVALESCENCE FROM SURGICAL PROCEDURES*

I. STUDIES OF THE CIRCULATION LYING AND STANDING, OF TREMOR, AND OF A PROGRAM OF BED EXERCISES AND EARLY RISING

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AND
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AFTER any operative procedure the patient for a time is obviously abnormal. He does not feel as he did in health, and he is unable to perform certain tasks which in health would be easy for him. Nevertheless, the routine hospital studies disclose nothing abnormal during this period of convalescence.

The purpose of this investigation was to search for objective abnormalities during convalescence from surgical procedures; by available special techniques, and by other methods which we might devise. If we could discover objective abnormalities they might be used as a test for the duration of convalescence and also as a means of judging the success or failure of attempts to shorten it, which were also part of our project.

In planning the work we expected that few abnormalities would be found when convalescent subjects were studied at rest, but we also expected that, by having them perform a task, abnormalities might well be discovered. For such a test, preferring tasks that our patients were accustomed to, we chose the following: the first test consisted of observing the changes in the circulation which took place on arising, the second, of studying the effects of mild exercise produced by pushing up and lowering a weight. Our results with the first will be given here; our experience with the exercise test will be reported in a paper to follow this.

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania.

Technique. All patients were from the surgical wards of this hospital, and they were operated upon by members of the two surgical services. The cases for herniorrhaphy all had spinal anesthesia; in the other cases the anesthetic varied and will be mentioned later. The standard operative techniques were employed.

Our method of testing for abnormalities of the circulation by its response to arising has been described,[10] and a large experience with this test[11] formed the background for the present study. The standard procedure used was as follows.

No tests were done within 2 hours after a meal. The subject lay at rest for at least 15 minutes on the horizontal ballistocardiograph. Blood pressure was then taken and also the "H" (horizontal) ballistocardiogram. The subject then arose, walked about 3 paces to the vertical ballistocardiograph, and stood upon its platform. Three estimates of blood pressures were made at intervals of about 2 minutes. The "V" (vertical) ballistocardiogram was taken about 2 minutes after the upright position had been assumed, between estimates of blood pressure.

Cardiac outputs were calculated from the ballistocardiograms by the area method.[9] Normal standards for this test have been published.[9]

All patients with hernia to be repaired were tested in both positions before operation, usually on the day preceding it. On the sixth day after operation they were tested again, the ones who had not yet left their beds being tested in the horizontal position only. All were tested in both positions on the tenth day, the day the majority were first permitted out of bed, and again on the two days following. After this they were discharged. There were occasional deviations from this schedule due to difficulty in performing the tests on Sunday, so sometimes a day elapsed between two of the last three tests. A few estimations were lost by accident.

The patients subjected to more serious operations were tested on the same schedule as far as possible, but some of them were never able to stand, and many remained in the hospital for a much longer time and were studied at intervals during their stay.

Approximately 200 position tests were made in the entire investigation, and the results have been subjected to statistical analysis, the calculations being made by the methods of Fisher.[2] Whenever the word "significant" appears in this paper, it is used in the statistical sense, indicating a probability of less than 5 in 100 that chance would account for the result.

Results. As the patients with hernia were in good physiological health before operation, any changes which occurred after operation could be confidently attributed to postoperative convalescence. This was not the case in many other types of patients, for operation was often followed by improvement in their general condition which overweighed the changes due to convalescence. Therefore the data obtained after herniorrhaphy were studied first.

Effect of Herniorrhaphy. To analyze our results the values found before operation were subtracted from the corresponding values found after it, the difference representing the change caused by the procedure. These changes were averaged, and their means and the standard deviations about the means are recorded in Table 1. A statistical test was then applied, using Fisher's "t" function,[2] to ascertain whether the means were significantly different from zero (also see Table 1).

An example will make our method clear. The resting pulse rate before operation in patient A was 75. Six days after operation it was 70. The change following the operation is −5. The average of similar changes in all our 25 patients on the sixth day was +2 (see

TABLE 1.—EFFECTS OF CONVALESCENCE FROM HERNIORRHAPHY ON THE CIRCULATION

Postoperative day of test	6th				10th				11th				12th			
	mean	σ	n	sig.	mean	σ	n	sig.	mean	σ	n	sig.	mean	σ	n	sig.
Subjects lying at rest:																
Pulse rate per min.	0	15	25	no	+1	15	25	no	+1	12	25	no	+2	11	22	no
Syst. B.P. mm. Hg	+2	11	25	no	−5	11	25	yes	−8	10	25	yes	−6	11	23	yes
Diast. B.P. mm. Hg	−2	12	25	no	−4	13	25	no	−7	12	25	yes	−5	10	23	yes
Cardiac output per min./lb. (average normal —100%)	−13%	19%	24	yes	−8%	21%	25	no	−7%	20%	24	no	0	15%	23	no
Subjects standing:																
Pulse rate per min.	+10	15	7	no	+9	13	22	yes	+5	10	24	yes	+5	15	22	no
Syst. B.P. mm. Hg	−12	14	7	no	−6	15	22	no	−6	12	24	yes	−8	12	22	yes
Diast. B.P. mm. Hg	−5	11	7	no	−4	18	22	no	−3	11	25	no	−1	8	22	no
Cardiac output per min./lb.	+14%	27%	5	no	+8%	30%	14	no	+10%	25%	21	no	+12%	24%	21	yes
Differences between lying and standing values:																
Pulse rate per min.	+2	11	7	no	+8	11	22	yes	+4	9	24	no	+2	10	22	no
Mean B.P. mm. Hg	−4	5	7	no	+1	8	21	no	+2	9	25	no	+1	8	22	no
Ratio { Cardiac output standing / Cardiac output lying	+21%	40%	4	no	+16%	22%	16	yes	+15%	17%	21	yes	+10%	16%	20	yes

The means are derived from differences between results found after and before operation. Thus the table shows that on the 10th day the systolic blood pressure averaged 5 mm. Hg lower than before operation. σ = standard deviation about the mean. n = number of cases studied. Yes or no = statistical significance for P = 0.05.

Table 1). This value is not significantly different from zero. The scatter of the results can be seen from the standard deviation (also see Table 1).

The data in Table 1 under the subheading, "Differences Between Lying and Standing Values," were derived as follows: in subject A before operation the pulse rate when he was horizontal was 72. After he arose, it was 86. The change on arising was therefore +14 before operation. On the tenth day after operation the corresponding values were 73 and 94, the change on arising being +21. The difference due to the operation in this patient is 21 − 14 = +7, and the average difference for all patients has been entered in Table 1. The data on blood pressure recorded in the lower one-third of Table 1 were derived the same way, but the changes in cardiac output on arising were calculated as ratios, and so the differences due to the operation are also expressed in per cent. The means and standard deviations in Table 1 have been rounded out to the nearest whole number.

Not all our data can be expressed in numbers and so entered in Table 1. Patients frequently had difficulty standing when they first arose from their beds. Some few could not stand at all, and many more stood but had so much tremor that the vertical ballistocardiogram was completely confused by it. This distortion of the record permitted a rough estimate of the amount of tremor, so a classification was made as follows: a perfect ballistocardiogram, *no tremor;* some distortion but not enough to prevent calculation of cardiac output at some place in the record, *slight tremor;* distortion so great that calculation of cardiac output is impossible, but systolic complexes can be identified sufficiently to count heart rate, *moderate tremor;* record completely confused by tremor, not even the heart rate can be counted, *marked tremor.*

To avoid unconscious bias, the records were arranged in a random order and presented to the senior author without anything to identify them. The results of his classification of the amount of tremor shown are given in Table 2. Obviously tremor in the upright position increases greatly after operation, but the abnormality largely disappears soon after the patients are up and about.

Effect of Exercise and Early Rising. Ten of the patients operated upon for hernia were treated differently from the others. Beginning with the second postoperative day these patients were placed on the following program which was carried out under the direction of a nurse each morning and again each afternoon for the duration of their stay in the hospital: for 5 minutes, while lying on their backs, they alternately flexed and extended first the wrists, then the elbows, then the shoulders in each of 3 directions, then the ankles, and finally the knees and hips together. Each joint in turn was flexed about 10 times in 20 seconds so that the series was repeated about 3 times in the 5 minutes allowed. The patients then stood beside their beds for 5 minutes and often walked a few steps. Then, after returning to bed, they repeated the exercises for 5 minutes.

The control group, following the usual hospital routine, took no

exercise and stayed in bed until the tenth day after the operation. Patients of both groups were tested on the sixth, tenth, eleventh, and twelfth days after operation.

To measure the effect of the exercise and early rising the subjects were arranged into pairs. For each exercised patient a mate was chosen from the unexercised group of the same sex and as near the same age as possible. All were males, and the ages of the 10 pairs were as follows: 45 and 46, 28 and 29, 33 and 31, 17 and 17, 21 and 18, 60 and 68, 37 and 29, 60 and 70, 26 and 24, 42 and 28.

The effect of the exercise on pulse rate, blood pressure, and cardiac output was estimated as follows: the change due to the operation was calculated for each patient by subtracting the value found before it. This value for the unexercised subject was subtracted from the corresponding value found for his exercised mate. The resulting difference, due to the exercise, was found for each pair, and an average for the 10 pairs was calculated. Finally a statistical calculation was made to determine whether this average was significantly different from zero.

An example will make the process clear. We have paired our patients, A and B; C and D, etc. A and C have been exercised, B and D not. The resting pulse rates before and 10 days after operation were for A, 80 and 84; for B, 75 and 78; for C, 65 and 64; for D, 73 and 76 per minute. The differences due to the operation were therefore +4, +3; and −1, +3. Now subtracting this value found in the unexercised B and D from that of their exercised mates, we have differences of +1 and −4 which may be attributed to the exercise. The average of these figures is −1.5. The average of our 10 pairs was −1.6, and by statistical methods we determine whether this value is significantly different from zero. A calculation similar to this was done on the measurements of pulse rate, blood pressure, and cardiac output made on each of the 4 days of the tests.

We will not report these results in detail because they were so largely negative. Nothing significant could be attributed to the exercise except on the tenth day after operation. On this day 3 of the unexercised patients were unable to stand, and 5 more had marked tremor, whereas all of the exercised patients could stand and only 1 had a moderate tremor. Tested by the method of χ^2 this difference is highly significant. In addition, the standing systolic blood pressure taken on the tenth day after operation averaged 13.4 mm. of Hg lower in the exercised group, and this was also significant. While the meaning of this blood pressure difference is not clear to us, we can conclude from the difference in tremor and ability to stand that the exercised patients were in better condition on this day. However, both significant differences disappeared by the day following, and we could find no other significant differences which could be attributed to the exercise in pulse rate, blood pressure, or cardiac output in either the horizontal or standing positions on any other day. This similarity of result is the justification for including both the exercised and the unexercised patients in same statistical analysis recorded in Table 1.

Results in Patients Convalescent from More Serious Operations. We studied 19 patients subjected to the following operative procedures: 3, exploratory laparotomy with nothing else done; 3, cholecystectomy; 3, colostomy, 2 for carcinoma, 1 for lymphopathia venereum; 1, lower esophagectomy for carcinoma; 3, gastric resection, 2 for carcinoma, 1 for ulcer; 1, gastrostomy for carcinoma of the esophagus; 3, craniotomy for tumor, for hematoma, and for exploration; 1, laparotomy for intestinal obstruction; 1, repair of mycotic subclavian arteriovenous aneurysm.

The anesthesias used also varied in the different patients: spinal, local, cyclopropane, nitrous oxide and oxygen, often with the addition of ether were employed. Postoperative complications such as fever occurred in some but not others. Treatment varied greatly, some patients receiving large amounts of fluids intravenously at operation and in the days following it, while others received none. Obviously the patients had so little in common that a study of the averages of our results would be meaningless. However, in most cases the trend of the results resembled those found after herniorrhaphy except where 1 of 2 factors entered into the situation.

Deviation from the usual postoperative pattern could often be attributed to the administration of large amounts of fluid given intravenously. This prevented the usual postoperative fall of cardiac output, and sometimes replaced it with a rise. Thus N. S., who had a gastric resection for carcinoma, received 13.5 liters of blood, and glucose, saline, or gelatin solutions intravenously within the week after operation. His resting cardiac output, + 4% above average

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LEGEND FOR FIG. 1.

FIG. 1.—Ballistocardiograms obtained in the horizontal position before and after operation. The time record on the top applies to all the records; its largest interval equals one second. The reproduction is actual size. *A*—L. A., age 26, 5 feet 8 inches, weight 146 pounds, a healthy person except for an inguinal hernia. Record obtained the day before operation. The calculated cardiac output did not deviate from average normal. The empirical normal limits are ±22%. *B*—Same subject on the sixth day after operation. The cardiac output is calculated to be −30%, a subnormal value. C—Same subject eleven days after operation. Cardiac output −4%. *D*—R. S., age 35, 5 feet, 75 pounds. Extremely emaciated from carcinoma of the pharynx. *First record* day before operation. Cardiac output −17% if calculated as the basis of her ideal weight, 118 pounds. *Second record*, nineteenth day after gastrostomy, cardiac output +22%. *E*—W. L., age 70, 5 feet 4 inches, 140 pounds. *First record* day before inguinal herniorrhaphy cardiac output −12%. *Second record* six days after operation is abnormal in form, the I wave being widened and shallow, approaching the segment of a circle in shape in contrast to the normal deep triangle. In the last complex shown the J wave is flattened and notched. Cardiac output cannot be estimated from such records. In records obtained on the tenth, eleventh, and twelfth day the ballistic form had returned to normal. *F*—H. J., age 66, 5 feet 8 inches, 111 pounds. *First record* day before exploratory laparotomy, cardiac output −19% referred to his ideal weight. Abdominal carcinomatosis found at operation, biopsy performed. *Second record* six days after operation. The form of most impacts is abnormal, the J waves being reduced in amplitude, notched or flattened. The form varies markedly from beat to beat. An occasional normal complex is seen. *Third record* 8 days after operation. The amplitude is larger, but the abnormalities in form remain the same. The patient died six days later. Necropsy found carcinomatosis, intestinal perforation and peritonitis. The heart weighed 300 grams. The muscle was firm, the chambers slightly dilated. The coronaries were patent although they contained sclerotic plaques. The valves were normal.

normal before operation, was + 22% above on the first test 11 days after it. After the extra fluid was stopped the circulation diminished to its original level. G. H., whose arteriovenous aneurysm was repaired,

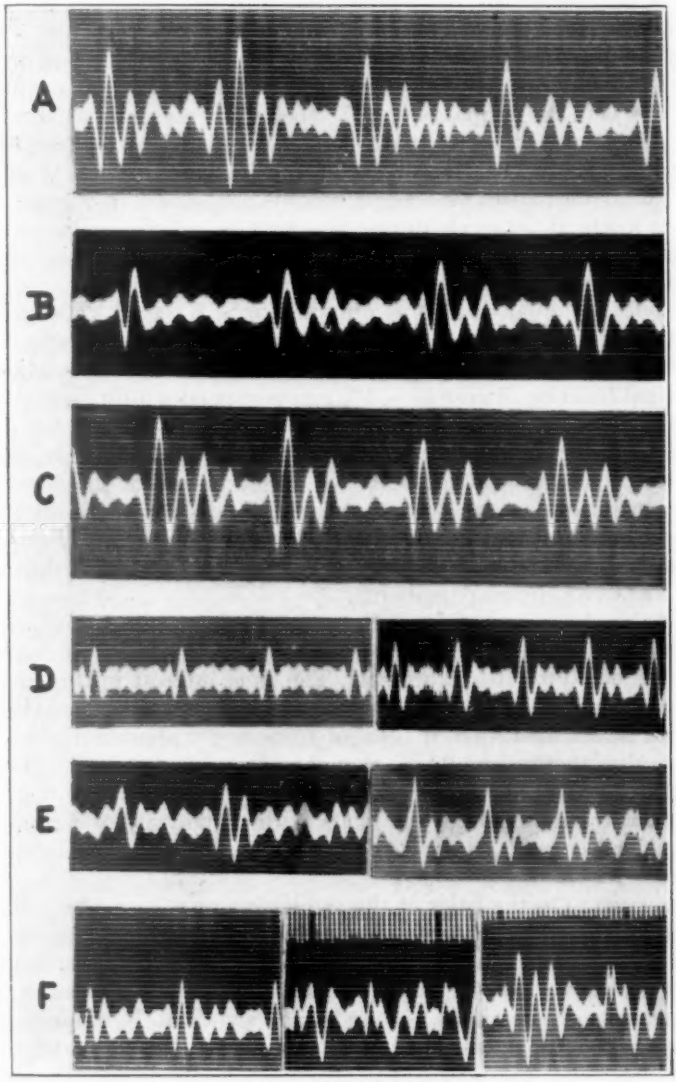

FIG. 1

received 5.1 liters intravenously at operation and during the day following. Her cardiac output, + 9% before operation, was + 39% on the second day after it, and gradually returned to the original level. M. H., who had a colostomy for lymphopathia venereum

received a total of 9650 cc. during the first 3 postoperative days. Her resting cardiac output tested on the sixth day after operation was the same as it had been before operation.

When the patient's ability to take food and fluids was improved by the operation, the postoperative course differed from the usual. Thus R. S., aged 35, and 44 pounds under her ideal weight, as a result of carcinoma of the pharynx, had a pulse rate of 83 and a blood pressure of 95/70 before operation. At this time her resting cardiac output per minute was in the normal range, 17% below average normal, if referred to her ideal weight. After gastrostomy permitted better feeding, the pulse rate rose to 118, the cardiac output increased to +17% and the blood pressure to 108/84. These records are shown in Figure 1. In 7 tests made at intervals during the next month the pulse rate and cardiac output remained at their high postoperative level, but the blood pressure diminished slowly until the preoperative value was regained. A similar result was obtained in S. B., aged 52, who had a colostomy for carcinoma. The resting cardiac output before operation was subnormal, −26%; after operation permitted more normal gastrointestinal function, it rose to −4% and remained within normal limits in the 5 tests made thereafter.

Three of our patients died. L. O., aged 51, died suddenly 18 days after the removal of a carcinoma of the lower end of the esophagus. After operation she was never able to stand or even to sit in bed without becoming dizzy and faint, these symptoms being accompanied by marked fall of blood pressure. Necropsy showed that death was due to a large pulmonary embolus.

H. J., aged 66, died 14 days after an operation for intestinal obstruction due to carcinoma. His blood pressure was 142/78 before operation and rose slowly to 164/90 after it. The chief interest in this case was in the change in form of the horizontal ballistocardiogram (Fig. 1). Normal before operation, it became increasingly abnormal after it, so cardiac dysfunction should be thought of as a factor in the terminal picture.

R. S. with carcinoma of the pharynx died suddenly of a rupture of an involved carotid artery 82 days after operation. The interest in this case has been mentioned.

Discussion. On the basis of the significant results one may draw a picture of the changes in the circulation which may be expected as a result of surgical operations and the bed rest which follows them.

When observations are made on patients in the *horizontal position*, cardiac output per minute is found to be significantly diminished for several days after operation, but it then slowly increases and by the day of discharge has returned to the preoperative level. The resting systolic blood pressure, unchanged for a short period after operation, becomes significantly diminished later, to rise somewhat before discharge. The resting diastolic blood pressure behaves quite similarly, but in our data the average remained significantly diminished to the end of our tests. The resting pulse rate is unchanged after operation. All these blood pressure and pulse rate changes are small, and none

of them would have attracted the attention of attending physicians employing the usual methods of examination.

When observed with the patient in the *vertical position*, the changes found after operation are more striking. Some patients cannot stand without fainting; others stand only with marked tremor which doubtless aids in supporting their circulation. The standing pulse rate averages 10 beats per minute faster when patients are first allowed to stand than before operation. This abnormality rapidly diminishes as the patient begins to be up and about the ward. Standing systolic blood pressure is lower after operation, but diastolic blood pressure remains unchanged. Standing cardiac output per minute is calculated to be higher after operation but was only significantly so in the last day of our tests.

Other abnormalities of convalescence can be demonstrated by studying the changes which occur when the subject arises. In normal persons the pulse rate always accelerates on arising, the average increase being 17 to 18 per minute.[7,10] In our patients, on the tenth day after operation, the day most of them left their beds for the first time, the pulse rate on arising increased on the average of 7.6 per minute more than it had before operation. On this same day the calculated cardiac output also increased more on arising than it had before operation, and this difference was significant. All these abnormalities disappeared within 3 days after the subject was up and about.

This picture of circulatory abnormalities in convalescence, drawn from our results on the patients operated upon for hernia, can be extended to those subjected to more serious operations with certain modifications. The more seriously ill patients often exhibited abnormalities of the circulation in the upright position before operation, and these were greatly increased after it, so that some patients were unable to stand without marked tremor and a greatly accelerated pulse rate for many weeks. In general, the abnormalities found after severe operations were identical with those recorded in Table 1 if they were not modified by 1 of 2 factors. First, the administration of large amounts of fluid after operation increased the cardiac output or prevented its diminution, an effect probably comparable to those found by Hardy and Godfrey,[4] and Fletcher, Hardy, Riegel and Koop[3] after the intravenous administration of saline solution and gelatin to dehydrated patients. Second, if the operation permitted better nourishment of the patient, the postoperative findings showed a picture strikingly different from that found before operation.

Abnormalities of ballistic form appearing for the first time after operation have been encountered twice in this study. One of these patients died; in the others the ballistic form returned to normal before discharge. Other instances of transient abnormality of ballistic form after operation have been published.[12] Thus we have evidence that operation can effect the heart adversely. However, such an effect is rare. In our experience it has occurred only in persons over 65 or in those with heart disease manifest before operation.

Certain of our results are consistent with those of other investigators

studying related problems; and as the whole field of convalescence has been recently reviewed,[14] the number of references needed here is small. Snyder[8] found a marked reduction of resting cardiac output in 4 of 7 patients tested on the first day after operation with recovery by the time of discharge. Our results are similar although our patients were first tested on the sixth day. Since certain of our cases receiving large amounts of fluid intravenously did not show this abnormality, one wonders whether reduction of blood and tissue fluid volume from hemorrhage, capillary leakage, sweating and the like, accompanied by low fluid intake were not the cause.

Most persons who have had an operation can testify to the difficulties and symptoms which beset them when they first arose from bed. We have found no previous study of the blood pressure and pulse rate on assuming the vertical position during postoperative convalescence, but similar abnormalities were found during convalescence from fever by Kopp.[6] The abnormalities of our convalescents when they first arose from bed do not differ from those found in many persons sick from a large variety of causes,[11] and especially in certain cases of neurocirculatory asthenia.[13] Inability of the peripheral circulation to adjust quickly to the additional demands put upon it by the upright position, with resulting cerebral anemia, is the explanation usually given and with this we concur, although the fact that the cardiac impacts were often large inclines us against the view that diminished cardiac output from a diminished venous return plays a part in the symptoms of such as these. That this mechanism may cause syncope under certain other conditions is not disputed.

Whatever may be the exact physiological abnormality which prevents proper adaptation to the standing position after operation, it is improved by practice. It took only a day or two of being up and about for the response to arising to return to normal in most cases. On the tenth day after operation those exercised and permitted out of bed from the second day onward were clearly more normal in this respect than those who had remained in bed until the tenth day.

Many of the abnormalities found in our patients after operation are similar to those demonstrated in healthy persons who have volunteered to remain in bed.[1,5] However, in the latter case the abnormalities usually developed after a much more prolonged bed rest than our patients had; and while we do not doubt that bed rest was a factor in our results, we believe that the operation itself played the larger part.

During the investigation we often asked ourselves whether the changes found after operation could be due, not to effects of the operation itself, but to apprehension of it, the emotional effect altering the circulation before operation and causing a change by passing off when the operation was over. The possession of normal standards for our test[11] aided in the identification of persons with severe emotional disturbances before operation. Inspection of Tables 1 and 2 show that the resting cardiac output, standing pulse rate and tremor, after changing from the preoperation level, returned to it again before discharge, so there seems no possibility that emotion could account for

these results. However, when the original level was not regained during the period of observation, as was the case with systolic pressure, the possibility that such an emotional effect entered into the result cannot be excluded.

TABLE 2.—TREMOR WHEN STANDING UPRIGHT BEFORE AND AFTER HERNIORRHAPHY IN 25 CASES

	Before operation	After operation		
		10th day	11th day	12th day
Unable to stand	0	2	0	0
Marked tremor	0	4	0	0
Moderate tremor	2	3	6	1
Slight tremor	15	13	12	16
No tremor	7	3	7	6
Not tested	1	0	0	2

The numbers given represent the number of patients in each category.

Our data permit an objective evaluation of the program of exercises in bed and early rising from bed that we tried. We obtained no evidence whatever that the exercised group was in anyway harmed by the more novel routine. Also, on the tenth day when the group in the regular routine was first allowed out of bed, the performance of the exercised patients was definitely superior. But it took only 1 day of being up and about for the group on the regular routine to equal the performance of those on the program of exercises and early rising, so we doubt whether anything very important was gained. The demonstration had the result of altering the routine handling of patients with hernia in the Hospital of the University of Pennsylvania, and many of them are now permitted out of bed on the third day after operation and sent home much sooner than had previously been the case.

The data obtained in this investigation permits conclusions about the objective detection of the convalescent state and, therefore, about methods for passing judgment on procedures designed to shorten convalescence. In this study we have had the great advantage of possessing data on our patients before they became convalescent. If one first saw the patient during convalescence, judgment of his state would be far more difficult.

For example, one of the most significant abnormalities we discovered is the change in pulse rate which occurs on arising. In healthy persons the average pulse rate increases 16.6 per minute when they arise;[10] on the tenth day of convalescence the increase is almost 50% greater than this. For healthy persons the usually accepted normal range, twice the standard deviation applied to both sides of the mean, extends from 0 to 33 per minute; that is, any person whose pulse rate on arising increases by any amount between 0 to 33 per minute would have to be regarded as normal.

A physician seeing the patient for the first time after operation would have data such as this on which to base his judgment, and, after ascertaining the lying and standing pulse rates in convalescents, he could use it. However, judging from our data obtained after hernior-

rhaphy he would detect an abnormality in only 22% of his cases. After more serious operations this percentage would be higher, but, obviously, the test is too crude to permit final judgment on the fitness of any person. It might be of some service as a first screening test, those failing being judged unfit, while those passing were considered well enough to take a more strenuous exercise test. A study of all our data on pulse rate, blood pressure, and cardiac output does not disclose any more promising basis for designing a satisfactory test for the presence, and so the duration, of convalescence in an individual first seen after operation.

When one is comparing two series of cases, however, a statistical analysis of tremor, blood pressure, pulse rate, and ballistocardiographic changes yields results on which conclusions can be based with confidence. The number of cases needed will depend, of course, on the size of the abnormality they develop, but some hints for future studies of convalescence can be obtained from our data. It is to be noted (Table 1) that only 7 of our subjects were tested while standing on the sixth postoperative day. The abnormalities found in these subjects were larger than on any other day, but their number was so small that statistical significance was not attained. With 20 or more subjects much smaller abnormalities were found significant. Series of this size should be sufficient and would permit detection of the objective manifestations of convalescence and so aid in the evaluation of methods designed to shorten it.

Summary. Forty-four patients have been studied before and repeatedly after surgical operations. The test used consisted of estimates of pulse rate, blood pressure, and cardiac output (ballistocardiogram) under standard conditions in both the horizontal and vertical positions. The results have been subjected to statistical analysis.

The average of results obtained in 25 cases operated upon for hernia disclosed that the following significant changes occurred during postoperative convalescence:

In the *horizontal position* cardiac output was diminished soon after operation, and blood pressure was diminished later. In the *vertical position* pulse rate was increased, cardiac output tended to be increased and systolic blood pressure to be diminished.

The difference between the lying and standing pulse rates, and the ratio between lying and standing cardiac outputs increased after operation. There was more tremor on standing, and occasionally subjects were unable to remain standing after operation.

After more serious operations the changes found in convalescence were generally similar to those described after herniorrhaphy with two exceptions. (1) The administration of large amounts of fluid by vein prevented the postoperative fall of cardiac output or caused it to increase. (2) If the operation permitted better nutrition of the patient, improvement from this cause far overbalanced the effects of the operation *per se*.

The scatter of the data was great enough to prevent the development of a simple test for the duration of convalescence which could

be applied to single individuals. Nevertheless significant comparisons could easily be made between small series of cases.

Ten cases of hernia were given a program of exercises in bed and early rising beginning with the second or third day after operation. Comparison with a group not so treated showed that the exercised group tolerated the upright position better than the controls when the latter were first allowed out of bed. This advantage lasted only for a day, however, so we doubt whether anything important was gained by the exercise program.

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CONVALESCENCE FROM SURGICAL PROCEDURES

II. Studies of Various Physiological Responses to a Mild Exercise Test

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The aim of this investigation was to explore the possibilities of finding objective methods of demonstrating abnormalities present in convalescence after surgical procedures which would serve as an indication of the duration of the convalescent state and as a test of measures designed to shorten it.

It was our belief that no abnormalities characteristic of convalescence would be demonstrable while the patients lay at rest, but we hoped that when they performed a task, abnormalities might manifest themselves. The first task assigned was the maintenance of the upright

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania.

position, and our experience with that test has been described in the previous communication.[11] In this paper we will describe our experience with a mild exercise test which could be applied to persons in bed.

The number of exercise tests in the literature is large,[9] but none of them seemed to meet our requirements. First, we needed a test which could be performed without danger of rupturing an unhealed abdominal incision. Second, to make the test generally useful we needed to limit ourselves to apparatus in common use in hospitals and to techniques which did not require unusual skill and training of the operating personnel. For the first reason, tests, such as stair climbing or riding the bicycle ergometer, were regarded as unsuitable for patients immediately after operation; and, for the second reason, we sought to avoid the apparatus and technique usually required for gas analysis. So we finally designed an easy weight lifting test which could be performed by the subject while lying in bed on his back and breathing from a spirometer designed to measure basal metabolic rate. By this means oxygen consumption could be determined without gas analysis and both rate and volume of respiration estimated from the spirometer record as well. We also counted pulse rate and in a few experiments took ballistocardiograms.

Estimations made during the exercise failed to demonstrate any significant abnormalities which could be attributed to the convalescent state, but observations made after the exercise was over demonstrated that the return to normal was significantly slower during convalescence.

Methods. *Subjects.* Five healthy persons were studied, the authors and two persons associated with other phases of the project.

The patients studied all came from the Surgical Clinic of this hospital. The operations were performed by members of the services of Dr. E. L. Eliason or Dr. I. S. Ravdin. A satisfactory study was completed on 20 patients of whom 12 were operated upon under spinal anesthesia for hernia. In the others, the operations performed were gastric resection in 3 cases; cholecystectomy in 2; appendectomy, choledochostomy, and intestinal resection for carcinoma in 1 each. All made satisfactory recoveries from the operative procedures.

Schedule. Every patient was tested before operation, and most of them several times afterward. The relation between the day of operation and the day of test varied somewhat more than in the previous study. Most patients were tested on the third or fourth day after operation, again on the ninth or tenth day, and finally about the seventeenth day if they still remained in the hospital. In all, 91 exercise tests were performed.

Exercise Tests. No test was made within 2 hours after a meal. The patient lay on his back either in bed or on the horizontal ballistocardiograph. A half face mask with a pneumatic cushion was held over nose and mouth by straps around the head, and its outlet was attached to a Benedict-Roth basal metabolism spirometer with a capacity of 5 liters, having valves and not a motor blower. The spirometer was filled with oxygen.

After a rest period of about 15 minutes the oxygen consumption was recorded for 4 to 6 minutes. Then, if the record was satisfactory, the subject was given a 10 pound iron bar, and a metronome was started ticking every second. With each tick the subject alternately raised and lowered the weight from his chest to arm's length above it. He thus raised it 30 times in a minute while continuing to breathe from the spirometer. After exercising thus for 1 minute, the exercise was stopped. The record of oxygen consumption was continued for the next 5 minutes or until the slope of the record became linear. Such a record is shown in Figure 1.

Oxygen utilization during the exercise was calculated as follows. After inspection of the record obtained before the exercise was started, a line was drawn as in the routine estimation of basal metabolic rate. This line is labeled 1 in Figure 1. During exercise the record sometimes moved erratically, and its form varied greatly from subject to subject. So in some cases this part of the record could not be used as basis for a line. However, within a few minutes after exercise had ceased, the record became linear once more so that a second line could be drawn. This line is labeled 2 in Figure 1. This second line was, as a rule, nearly parallel with the first line, but it was not a continuation of the first line. If extrapolated to the right, the second line lay above the first because of the extra oxygen consumed during and immediately after the exercise. To estimate this extra oxygen the adjacent ends of lines 1 and 2 were joined by a third line (line 3, Fig. 1) drawn regardless of the record. This third line extended over the record obtained during the minute of exercise and over the period after it during which the oxygen debt was being paid. It is labeled 3 in Figure 1.

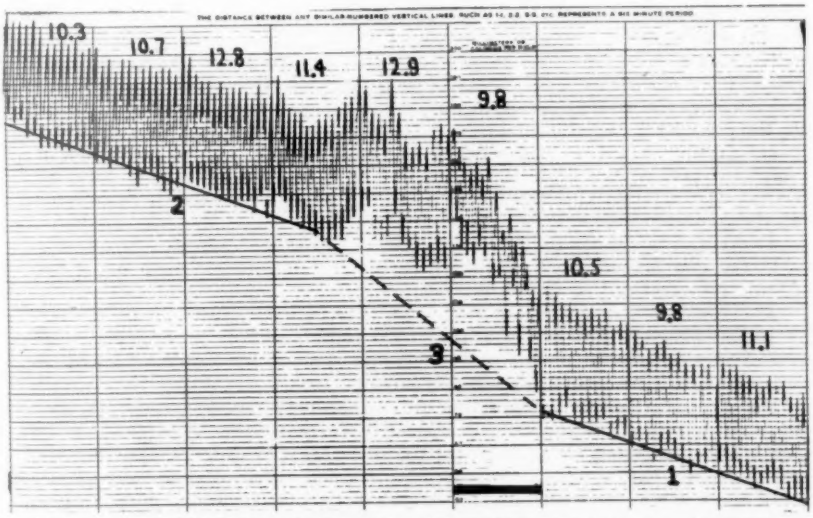

FIG. 1.—Record obtained on Patient G. F. (age 30, height 5 feet 5 inches, weight 138 pounds) with a Benedict-Roth metabolism spirometer before and after exercise on the 14th day after operation. Read from right to left. The bar shows the duration of the exercise (1 minute). The numbers beneath the record refer to the lines drawn to estimate oxygen consumption. The numbers above the record are the respiration in liters per minute. The record ran for a longer period both before and after exercise than is shown in the illustration.

In certain records there was some doubt where the junction of lines 2 and 3 should be placed. However, since lines 1 and 2 were usually parallel or nearly so, the position selected for this junction made little or no difference to our calculations of the oxygen required for the exercise.

From these 3 lines the extra oxygen needed for the exercise was calculated. By the usual methods used for estimating metabolic rates, we estimated oxygen consumption in terms of dry gas under standard conditions and applied the results to our problem as in the following example:

From the data given in Figure 1 we calculate:

1. Oxygen consumption before exercise (from line 1) = 208 cc. per minute.
2. Oxygen consumption when, after exercise, the record has become linear (from line 2) = 213 cc. per minute.

3. Average oxygen consumption over the two and one-half minute period of exercise and recovery (from line 3) = 480 cc. per minute.

We may interpret this data as follows:

1. Oxygen consumption at rest: 208 cc. per minute.
2. Oxygen consumption during exercise: 480 cc. per minute.
3. Extra oxygen consumption needed for exercise: 480 − 208 = 272 cc. per minute.
4. Duration of exercise and recovery period 2.5 minutes.
5. Total extra oxygen used for exercise 272 × 2.5 = 680 cc.

We naturally had most confidence in the result when lines 1 and 2 were parallel or nearly so. In some cases, however, these lines diverged, and then it was hard to be certain how best to handle the data. There were two possible methods. The resting oxygen consumption could be calculated from the average of the values found before and after exercise, obtained from lines 1 and 2. This was usually satisfactory enough, but occasionally we obtained the surprising result that no measurable oxygen was used in the exercise, a phenomenon which does happen in certain diving animals and in the sloth.[6,7] However, when the resting oxygen consumption was calculated from line 1 only, this result was obtained only twice; so we came to prefer this method, and it is used in the example given above.

Occasionally we were left in doubt whether the oxygen debt had been fully paid by the end of the test. In some such cases we often prolonged the record by refilling the spirometer with oxygen, but, nevertheless, complete return to the pre-exercise level did not always take place during the period of observation. In such a case we finally decided to add the extra oxygen consumed in a standard period, the first 5 minutes of line 2, Figure 1, to that consumed during the exercise and the recovery period which immediately followed it. In these cases the calculation was made as follows:

1. Oxygen consumption before exercise = 230 cc. per minute.
2. Oxygen consumption during exercise and immediate recovery period (2 minute duration) = 420 cc. per minute.
3. Oxygen consumption for next 5 minute period = 240 cc. per minute.
4. Extra oxygen for exercise period, (420 − 230) × 2 = 380 cc.
5. Extra oxygen for next 5 minutes (240 − 230) × 5 = 50 cc.
6. Total oxygen used in exercise = 430 cc.

We are by no means certain that this is the best way to handle the data, for it is possible that the exercise changed the resting metabolic rate of our subjects by arousing them and so introduced an error into our results when calculated by this method.

In short, while there seemed no perfectly satisfactory method of making the estimation from some of our records, the errors involved were probably small. We tried several methods of making the calculation and found they made no material difference to the conclusions that could be drawn from our data.

The duration of increased oxygen consumption after exercise was measured from the end of the exercise period to the resumption of the resting metabolic rate at the junction of lines 2 and 3. This duration was often not easy to measure with great accuracy, and we were content to estimate it to the nearest ½ minute. Change in the mid-position of the diaphragm during exercise, as is shown by the record in Figure 1, increased the difficulty of the measurement, but this complication occurred in very few cases.

Respiration was estimated by measuring the up-strokes on the record and applying the calibration of the spirometer. The figures given in the tables represent the volume as measured over water in the spirometer. The temperature of gas in the spirometer was always recorded, and the median value was 25° C. In the series of tests done on any individual the range of the spirometer temperatures was so small that we have not corrected the data for it. The extra volume of respiration induced by the exercise was calculated in a manner similar to that used for extra oxygen, as follows:

In the record shown in Figure 1 we find:

1. Respiration before exercise, average of 3 minutes = 10.5 liters per minute.

2. Respiration during exercise and recovery period, average of 4 minutes = 11.7 liters per minute.
3. Respiration during last 2 minutes = 10.5 liters per minute.
4. Extra respiration needed for exercise 4 (11.7 − 10.5) = 4.8 liters.

As the respirations after exercise often varied from minute to minute, it was difficult to determine the exact time at which the pre-exercise level was regained. Hunt and Dufton[5] had the same experience, so following their example we calculated a "dyspnea ratio" as follows. Respiration during the exercise and for the first minute after it was neglected. The volume of respiration for the second, third, and fourth minute after exercise was taken and divided by the volume for the 3 minutes which preceded the exercise. Statistics for this quotient are entered in Table 6. Our quotient differs from that of Hunt and Dufton[5] as they measured respiration for one minute longer than we. After the much more vigorous work test they employed, this was doubtless advantageous, but inspection of our data suggested that the increased breathing was often over by the fourth minute after the mild exercise we employed.

Ballistocardiograms[10] were made before and after the exercise in some, but not in all subjects. During the exercise impacts from the patients' movements destroyed the record of the cardiac impacts, so estimations of cardiac output during exercise were not possible. We obtained satisfactory records within a few seconds after exercise was over. Therefore, the record was started when exercise was stopped and let run for about a minute. Another record was taken 5 minutes later.

Inspection of the records obtained in the first cases showed so little that could be attributed to convalescence that ballistocardiograms were omitted from the latter part of the study. This simplication permitted us to apply the exercise test to patients without moving them from the ward.

Pulse rate before and after exercise was counted from the ballistocardiogram or taken at the wrist.

Statistical Calculations. The methods of Fisher[4] were followed. Whenever the word significant is used in this paper, it is used in the statistical sense of indicating that the probability that chance would account for the result was less than 5 in 100. Thus, when the word "significant" is used, the reader should realize that a calculation to determine it was made, although the calculation itself may not be mentioned.

Results. To gain experience with the test we first used it 12 times on 5 *healthy persons* (Table 1). From the averages (Fig. 2) it is apparent that, as one would expect, the exercise was followed by increased oxygen consumption, respiratory volume, cardiac output, and heart rate. The effect on respiratory rate varied; subject L. S., who had been a sprinter in his youth, once held his breath for a large part of the exercise period. In many experiments the oxygen debt was so small that its payment after exercise could not be detected. In some cases this was obviously due to an artefact, for changes in the mid-position of the diaphragm during exercise made it impossible to decide how much oxygen was consumed and how much merely taken into the lungs in any given minute. Thus, records similar to Figure 1 would lead to an overestimation of oxygen consumption during the minute of exercise and an underestimation during the recovery period; but, as the diaphragm eventually returned to its former position, the total oxygen consumed during the exercise and recovery period can be estimated accurately. However, in most records the mid-position of the diaphragm did not change, and the minute to minute oxygen consumption could be measured with reasonable confidence.

TABLE 1.—EFFECT OF A STANDARD EXERCISE TEST ON NORMAL SUBJECTS

Name sex age ht. wt.	Date 1944	Oxygen consumed (cc. per minute)				Respiration: Volume (liters per minute)				Respiration: Rate (per minute)				Circulation: Cardiac output (deviation from average normal, %)			Circulation: Pulse rate (per minute)		
				After				After				After							
		Before	During	1st and 2nd min.	Last	Before	During	1st and 2nd min.	Last	Before	During	1st and 2nd min.	Last	Before	Immed. after	5 min. after	Before	Immed. after	5 min. after
R. M.	9–14	263	670	236	236	7.2	19.5	8.3	7.5	9	12	9	10	+13	+17	− 9	74	79	61
M 28	9–20	286	286	286	286	10.1	19.0	10.4	8.7	11	11	9	9	+ 9	+35	−22	68	110	61
6′ 2″ 175 lbs.	9–27	248	854	273	273	8.8	16.4	10.2	9.1	9	15	10	10	− 9	+17	−13	62	82	59
L. S.																			
M 30	9–19	310	521	267	267	9.3	13.5	10.6	9.6	10	12	9	10	+ 4	+26	+13	69	90	72
5′ 10″ 158 lbs.	9–20	231	620	236	236	9.5	10.9	9.3	9.2	10	9	8	10	+ 9	0	− 9	68	72	64
I. S.	9–12	252	718	224	224	7.7	16.9	9.2	8.0	12	11	12	12	+17	+30	+17	77	83	82
M 49	9–15	258	511	256	256	7.0	15.0	7.8	7.2	10	9	11	10	+ 9	+13	+35	79	79	79
6′ 0″ 185 lbs.	9–18	217	365	342	235	6.9	16.4	8.5	8.3	10	14	10	10	+13	+26	+22	72	80	76
M. G.	9–21	238	494	284	284	11.8	14.4	11.7	10.8	10	13	10	11	+ 4	+22	0	83	88	76
F 39	9–22	286	479	276	276	10.8	13.9	12.0	11.1	11	15	11	11	− 9	+26	−13	71	88	67
5′ 7″ 132 lbs.	9–26	243	430	309	231	9.6	11.9	11.5	10.5	10	10	11	12	− 9	+ 9	−13	64	63	60
M. B. F 42 5′ 9″ 125 lbs.	10–5	217	344	288	202	16.3	11.5	11.6	11.0	16	16	16	18	+13	+35	+17	67	70	65
Average	...	254	541	270	251	9.1	14.9	10.1	9.3	10.7	12.3	10.5	10.0	+ 5	+ 1	+ 2	71	82	69

Inspection of the results obtained on the same person on different days (Table 1) shows a high degree of variation. On September 20, R. M. apparently performed the test without using any extra oxygen from the spirometer; one notes that before exercise on this day his resting respiration and oxygen consumption were larger than in any other test. The effect of the exercise on cardiac output was also variable; on September 20, we demonstrated no increase in cardiac

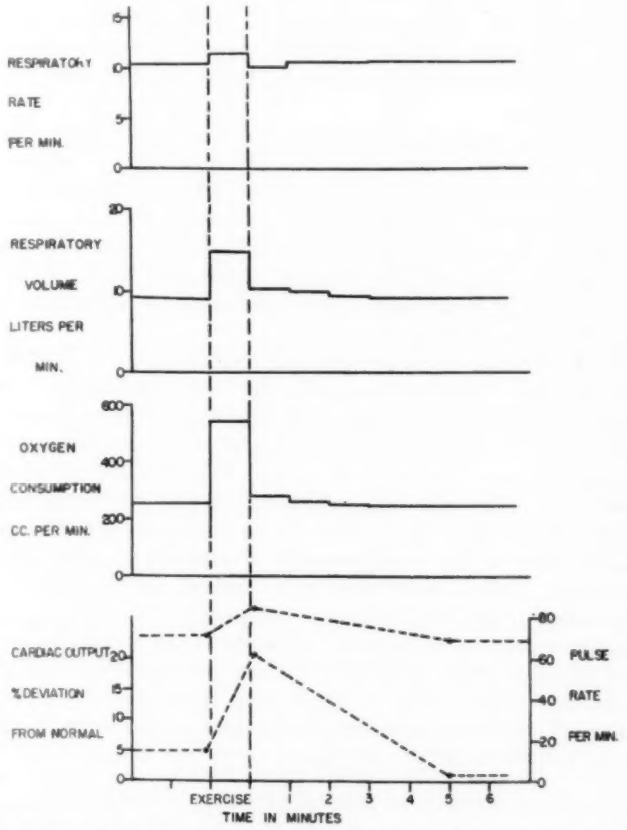

FIG. 2.—Average of the results obtained before, during and after exercise in 5 normal subjects who performed a weight-lifting test of approximately 600 foot-pounds for 1 minute.

output after exercise in L. S.; on September 15, I. S. showed a delayed effect. Such variations warned us that it would be difficult to draw significant conclusions from the results, but at this stage in the investigation it was conceivable that the effect of the surgical procedure would be great enough to outweigh the inherent variability of the responses to exercise.

The averages of our results on respiration and oxygen consumption after work are in agreement with expectations based on other

studies.[1,2,3,9,12] The work performed by our healthy subjects was much less than in most similar studies and their respiration and oxygen consumption were proportionally less also, so that the average ratio between work performed and oxygen consumption was essentially similar to that reported by other authors.

Using the usual method of calculation, the mechanical work performed by our subjects was approximately 600 foot-pounds per minute. The average oxygen required for the performance of this work by our normal subjects was 318 cc. Converting both work and oxygen to calories in the usual manner,[13] the average mechanical efficiency of our healthy subjects was 12.7%, a value close to that found in other weight-lifting tests.

When we tested *patients*, distortion of the results by emotion occurred frequently. This was manifest by the abnormally large resting oxygen consumption, and in 9 patients this finding forced us to abandon the test. Occasionally a patient who had performed in a satisfactory manner before operation was excited at a later test. In the tests whose results we accepted, the resting metabolism was always within or very near the normal basal range although we were not working under strictly basal conditions.

The results obtained *on patients* are summarized in Tables 2, 3, 4, 5, and 6. For statistical analysis the tests made after operation have been divided into groups. When oxygen consumption and respiration were studied, the most natural division of the data was into 3 groups of tests, these made 2 to 6, 7 to 11, and 12 to 21 days after operation. The data on cardiac output and pulse rate, however, were subdivided differently. Only few estimations of cardiac output were made because the early results looked so unpromising. The pulse rate data looked more promising, and we added several experiments in which pulse rate alone was measured. Accordingly data on the circulation were divided into 2 groups, those made 1 to 8 days and 9 to 19 days after operation. When more than one estimation was made on a single subject within one time period, these results were averaged so that n, as given in the tables, represents the number of patients, not the number of tests.

TABLE 2.—CHANGES IN RESTING VALUES DUE TO OPERATION

Date of results:	2nd to 6th day			7th to 11th day			12th to 21st day		
	mean	σ	n	mean	σ	n	mean	σ	n
Resp. rate per min.	+2.8	4.8	10	+1.1	1.9	12	+1.3	2.6	11
Resp. volume, liters per min.	0	1.6	9	+0.1	0.6	11	+0.3	0.7	11
Resting metabolic rate, deviation % normal basal	−3	11	8	−2	17	10	−10	25	10

The statistics are derived from differences between results found after operation and those obtained before it. For example, in tests performed between the 2nd and 6th day after operation, the average respiration rate was 2.8 per minute greater than it had been before operation. None of the means is significantly different from zero.

The data obtained on our patients give information about the effect of convalescence from operative procedures on resting respiration and oxygen consumption which supplements our previous study on the resting circulation. These are recorded in Table 2.

TABLE 3.—ABSOLUTE VALUES FOR EXTRA OXYGEN CONSUMPTION AND EXTRA RESPIRATION DUE TO EXERCISE

	Before operation			Days after operation: 2 to 6			7 to 11			12 to 24		
	mean	σ	n	mean	σ	n	mean	σ	n	mean	σ	n
Extra oxygen, cc.	271	161	15	311	122	10	420	207	11	422	179	11
Extra respiration, l.	4.9	5.7	15	4.3	6.6	10	7.7	4.9	12	5.5	4.2	10

Statistics from data obtained during a mild exercise test.

TABLE 4.—CHANGES IN THE RESPONSE TO EXERCISE IN POSTOPERATIVE CONVALESCENCE

Date of results:	2nd to 6th day			7th to 11th day			12th to 21st day		
	mean	σ	n	mean	σ	n	mean	σ	n
Extra oxygen required for exercise in cc.	−25	188	10	+41	168	11	+41	207	11
Extra respiratory volume required for exercise in liters	−0.5	11	10	+2.1	9	12	+1.8	7	10

The statistics given are derived from differences between results found after operation and those obtained before it. For example, in tests made from the 7th to the 11th day after operation, the average oxygen needed to perform the work was 41 cc. greater than before operation. None of the means is significantly different from zero.

TABLE 5.—CHANGES IN THE RESPONSE OF THE CIRCULATION TO EXERCISE DURING CONVALESCENCE AFTER OPERATION

	1st to 8th day			9th to 19th day		
	mean	σ	n	mean	σ	n
Pulse rate per minute:						
Immediately after exercise	−3.0	7.9	11	−2.5	7.1	13
30 seconds after exercise	−0.6	6.2	10	+1.1	5.5	13
5 minutes after exercise	+5.1	8.0	11	**+4.4**	6.8	13
Cardiac output:						
Immediately after exercise, %	+2.0	4.0	5	−1.0	4.2	6
30 seconds after exercise, %	+5.0	2.8	5	+2.0	3.1	6
5 minutes after exercise, %	+3.0	5.4	5	−3.0	0.7	5

The statistics given are derived from differences between results found after operation and those obtained before it. For example, in data obtained between the 1st and 8th day after operation the pulse rate 5 minutes after exercise averaged 5.1 per minute faster than before operation. The mean in bold face type is significantly different from zero.

TABLE 6.—CHANGES IN THE "DYSPNEA RATIO" AND IN THE "DURATION OF INCREASED OXYGEN CONSUMPTION" AFTER EXERCISE IN POSTOPERATIVE CONVALESCENTS

	Days after operation: 2 to 6			7 to 11			12 to 21		
	mean	σ	n	mean	σ	n	mean	σ	n
Dyspnea ratio	+0.4	0.08	9	**+0.8**	0.10	10	−0.3	0.12	9
Duration of incr. oxygen consumption, min.	+0.94	1.46	9	**+0.95**	1.04	10	+0.5	0.77	10

Means in bold face type are significantly different from zero.

To give readers a better idea of the results obtained with the exercise test the data have been recorded in two ways. In Table 3 statistics on the extra oxygen and respiration needed for the standard exercise are given, the averages being derived from data set up as are those in Table 1. This provides readers with a much needed impression of the nature of our results, but it is a poor method of arranging the data

for statistical analysis, and no one would be surprised to find that, as in this instance, the differences are not significant. In Tables 4, 5, and 6 the data are presented in such a way as to neutralize individual differences which may be present. In these compilations the values for each subject found before operation have been subtracted from the corresponding values found after it. The averages of these differences are given in Tables 4, 5, and 6, and one can thus ask himself the question whether the average change caused by the operation is significantly different from zero. This same method was used in the preceding paper, where an explicit example is given.

In analyzing the data on oxygen consumption and respiration we studied both the absolute values and the values per square meter of body surface. No improvement in the scatter resulted from the inclusion of the latter factor nor was significance attained, so the figures given in the tables are not divided by body surface.

Discussion. In a previous investigation we studied the effect of operative procedures on the circulation of resting subjects. Although not our primary object, the studies reported here permit us to add information about the effect of operation on the resting respiration and oxygen consumption. These data are summarized in Table 2, and statistical analysis shows that none of the changes found after operation is significant. It may be concluded, therefore, that the operative procedures had no effect on the respiration and oxygen consumption of subjects at rest.

The main purpose of this investigation was to answer the question whether the response to exercise was altered in postoperative convalescence. We speculated that a given amount of work might then be performed less efficiently, that is, with a larger consumption of oxygen in relation to the work performed, as has been demonstrated after more severe exercise when the performer is "out of condition."[9] From personal experience the senior author believed that when unwell, he tended to breathe more heavily for a given exercise than when in good health, so it was expected that respiration during a standard exercise would be greater during postoperative convalescence than before or after it. Our results, however, must be considered under two headings: (1) those concerned with the *amount* of the changes induced by the exercise and, (2) those having to do with the *duration* of these changes. The results of the first group were negative; that is, we were unable to demonstrate that convalescence had a significant effect on the amount of oxygen consumed, the mechanical efficiency, the volume of respiration, cardiac output, or pulse rate during mild exercise.

It is true that the average of these results is of some interest. Thus the average mechanical efficiency with which our patients performed the work was 10.9% before operation, 13% shortly after it, and then declined to 9.6% for the remainder of their stay in the hospital. Though the differences are not significant, one cannot but wonder whether the strain of the operation called out bodily reserves which at first increased the efficiency. Only after some days had elapsed was the reduced efficiency characteristic of convalescence revealed. The statistical

odds are almost 3 to 1 in favor of a decline in efficiency after the first postoperative week. If we had continued our work and studied a larger series of patients, significant differences might well have been attained. Our aim, however, was not to establish the decline in efficiency in convalescence, it was to devise a test for convalescence. For this purpose we have gone far enough to get our answer; no satisfactory test for convalescence can be developed by measurements of this kind. The variability inherent in the responses of individual subjects overwhelms the small changes which are caused by convalescence, and the latter frequently cannot be detected.

Our data on the duration of the changes induced by exercise contrast with our inability to demonstrate significant differences in the amount of these changes. During convalescence pulse rate, respiration, and oxygen consumption, although not unduly increased by the exercise, return to normal more slowly after it than was the case before operation. Thus the average dyspnea ratio,[5] a measure of the prolongation of increased respiration, is increased during convalescence. Reaching a maximum in the 7th to 11th day after operation the difference is significant at that time; later the abnormality diminishes as the patient improves. Similarly, after operation the increased oxygen consumption of exercise returns to normal more slowly as the subjects take longer to pay their debt. Again this abnormality reaches a maximum in the period between the 7th to 11th day after operation when significance is attained, to decline as the patient improves.

Also, after operation, while the average pulse rate taken within 30 seconds of cessation of exercise is not abnormal, that taken 5 minutes later is faster during convalescence than it was before operation. In the first week after operation the average difference just misses significance, the probability being 7.5 in 100, while in the following period significance was attained.

Obviously the objective abnormalities of convalescence are to be sought in the duration of the effects of exercise rather than in their amount. This is in accord with the observations of others in many conditions of ill-health.[9] The slow return of the pulse rate to normal after exercise has been the basis of many fitness tests. Increased dyspnea ratios have been reported in the unfit,[5] and a prolongation of the time required to pay the oxygen debt is a well known feature of heart disease.[8]

While we have been able to demonstrate significant abnormalities in convalescence by the use of averages, it is another matter to design a test which would detect these abnormalities in an individual seen for the first time in that state. The variability of the responses of our subjects was so great that we see no possibility of designing a satisfactory test for the detection of convalescence, and so of its duration, by a test of the type we have employed. Perhaps this should have been expected as abnormalities not detected by mild exercise could be demonstrated by more vigorous exercise in Hunt and Dufton's series. However, we question whether it would be proper to subject patients recently operated upon to exercise as severe as these authors employed.

Since the effects of postoperative convalescence are so overwhelmed by the variation inherent in our subjects, it was natural that we should give thought to the causes of this variation. One such cause, inherent in all weight-lifting exercise tests, consists of the differences in the way the work was done. In our test we can easily calculate the mechanical work performed, 600 foot-pounds per minute in each test. However, the conclusion that this value truly represented the effort exerted by the subjects would be erroneous. Other factors are of great importance. For instance, the calculation assumes that the bar is lowered without effort, which is certainly not the case as the subject opposes its free fall so that it will not strike his chest. To lift the bar with a jerk requires more effort also than if it is done with an easy motion, so the true effort exerted cannot be readily measured, and we have no assurance that our subjects were applying exactly the same effort in successive tests. That the manner of doing work affects the efficiency of a muscle's performance is well known.[9,13]

Attracted by the result obtained on R. M. on September 20, we calculated the correlation coefficient between the volume of respiration per minute before exercise and the extra oxygen needed for the standard exercise. Using all our data obtained on both normal subjects and patients, both before and after operation, we found significant negative correlation between these values. Apparently in our subjects deep breathing before exercise was followed by more efficient performance of mechanical work, and this raises some interesting physiologic questions far beyond the scope of this investigation.

We also sought for a relation between the oxygen consumption before exercise and the efficiency of its performance, but we found nothing significant.

Summary and Conclusions. By means of a standard mild exercise test we have sought for abnormalities during convalescence from surgical procedures.

Oxygen consumption, and volume, and rate of respiration have been determined before, during, and after standard exercise. Cardiac output (ballistocardiogram) and pulse rate were estimated before, just after, and 5 minutes after the same standard exercise.

Measurement of the *magnitude* of the changes induced by the exercise, revealed no significant differences which could be attributed to convalescence. However, when attention was given to the *duration* of the changes induced by the exercise, the averages showed significant differences, the increased oxygen consumption, respiration, and pulse rate declining to the resting level more slowly during convalescence than before operation.

The respiration and oxygen consumption of subjects at rest were not significantly changed during convalescence.

The variability in the physiologic response to exercise was so large that a test of the type used gives no promise of providing a satisfactory measure of the duration of convalescence in individual cases. However, the slow return to normal of pulse rate, respiration, and oxygen consumption after exercise is over may have some value as an indica-

tion of persisting abnormality in certain individuals and will provide significant differences when data obtained from a series of 10 or more cases are averaged.

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COARCTATION AND ACUTE DISSECTION OF THE AORTA ASSOCIATED WITH PREGNANCY

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The present report is that of a case of coarctation of the aorta with a dissecting aneurysm in a 23 year old pregnant white woman. Instances of coarctation of the aorta associated with pregnancy are unusual: Mendelson,[1] in a review of the literature in 1940, was only able to find 26 cases and added 3 cases of his own; a more complete review has uncovered 9 additional cases[2] besides the one reported here, bringing the total number of reported cases of associated pregnancy and coarctation of the aorta to 39. However, dissection of the aorta occurred in only 2 of these cases, those reported by Strassman[3] and by Katz.[4] The present case, then, is the third in which dissection occurred in coarctation of the aorta in a pregnant woman and is the first in which the diagnosis was made before death.

Case Report. The patient, a 23 year old white, married, pregnant woman (K 1178) entered the Newton Hospital, Feb. 10, 1944, on the orthopedic service because of severe pain in her neck that extended down her left arm.

The patient stated that she was 6½ months pregnant. She had had frequent examinations during this period and was told that her blood pressure and

urine were normal. The pressure recordings were 140/90, 120/70 and 144/80 during the 3 months before admission. Six days before the present episode she visited a local obstetrician to make arrangements for further prenatal care and delivery. At this time, physical examination revealed a slight systolic murmur over the base of the heart which was interpreted as a functional murmur. It was thought the thyroid gland was somewhat enlarged. No pulsation was noted in the right neck. The blood pressure in the right arm was 160/100. No other abnormalities were noted at this time.

On the morning of admission she was stooping over a sink about to wash her hair when she was called and lifted her head suddenly with a sideways motion. This was immediately followed by sudden pain in the back of her neck extending from the occiput down the spine to a point midway between the scapulæ. Pain was also experienced down the left arm as far as the elbow and in the back of her throat. The pain was dull in nature but steadily increased in severity. It was not aggravated by motion. She was able to move her head in all directions except extreme flexion. Rest did not improve the condition. A buzzing sensation developed in her right neck. The patient became apprehensive and a physician was summoned who advised hospitalization.

The *family history* was not remarkable. The patient's mother, father and four brothers were living and well.

The *past history* showed that development was normal. She had always been active in sports and had noted no symptoms except for a pulsation in her right neck following exertion. As a child she had mumps, whooping cough, scarlet fever and chicken-pox. She had no other illnesses except a history of joint pains at the age of 16 that did not confine her to bed.

Present History. On admission the pulse was 64, temperature 98.4° and respirations 20. The blood pressure in the right arm was 100/90 and in the left arm 138/88. No readings could be obtained in attempting to take the blood pressure of the legs. The skin of the face seemed somewhat suffused. There was a slight fulness over the thyroid area. There was a marked pulsation in the right side of the neck at a point just above the junction of the sternocleidomastoid muscle and clavicle, and a palpable thrill and systolic impact over this area. Posteriorly, there was tenderness over the cervical vertebræ. There was moderate limitation of flexion of the neck but movements of the neck were not restricted otherwise. The breasts showed only the usual changes associated with pregnancy. Lungs showed no râles but there was slight dulness and decreased breath sounds at the right base. The heart was enlarged to percussion both to the right and left with increased dulness at the base of the heart, especially at the left upper border of the breast. The rhythm was regular and the sounds were forceful and of good quality. A Grade II systolic murmur was heard over the base, especially at the pulmonary area, and a fainter systolic murmur at the apex. There was an impact to the sounds at the base. A faint but definite systolic murmur was heard between the vertebræ and the spine of the left scapula. A pulsating artery was felt beneath the rib in the left midback. The radial pulse on the right was weak and was of normal intensity on the left. Pulsations were absent in the abdominal aorta, femoral arteries and dorsalis pedis vessels. There was no pitting edema. The abdomen was enlarged and the fundus of the uterus was palpable just above the umbilicus. The fetal heart sounds were of good quality, the rate being 140.

Laboratory Data (during hospital stay). Hemoglobin, 78% (Sahli); red blood cell count, 3,590,000; white blood cell count, 13,900; a normal distribution of the white cells and no abnormal red or white blood cells. The N.P.N. was 38.8 mg. and the blood cholesterol 259.2 mg. per 100 cc. The fasting blood sugar was 107 mg. per 100 cc. The blood Hinton was negative. Two electrocardiograms (Feb. 11 and 14, 1944) showed slight left ventricular preponderance; the second showed slight but definite elevation of $ST_1 + ST_2$ and slight depression of ST_4 (Fig. 1). Roentgen ray of the chest on the 1st hospital day showed the heart to be enlarged and the lungs to be clear; the 4th

and 5th hospital days, Roentgen rays showed a further increase in the size of the heart and width of the mediastinal shadow (Fig. 2).

Hospital Course. The patient was seen by one of us (S. A. L.) who made a diagnosis of congenital coarctation of the aorta with acute dissecting aneurysm. At this time she appeared fairly well. The patient was moved out of the general ward into a single room and arrangements were made to perform an

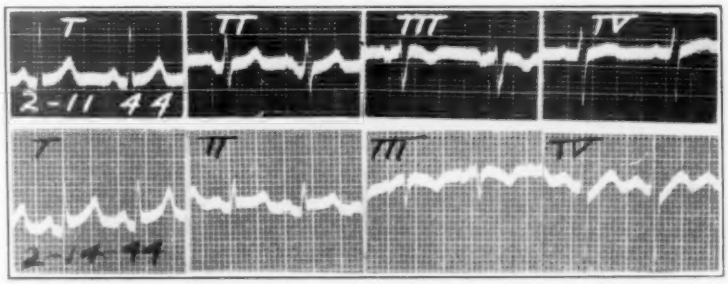

FIG. 1.—Upper electrocardiogram (4 leads) taken Feb. 11, 1944; lower record taken Feb. 14, 1944. Note slight elevation of ST_1 and ST_2 and slight depression of ST_4.

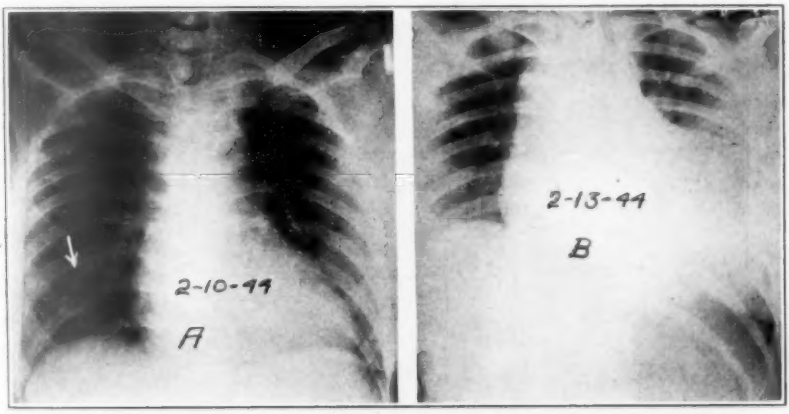

FIG. 2.—*A*, a 7 foot Roentgen ray plate, taken Feb. 10, 1944, shows moderate general cardiac enlargement and some prominence of ascending aorta. There is slight but definite notching of the ribs especially of the right eighth rib posteriorly. (See arrow.) *B*, Roentgen ray (bed plate taken Feb. 13, 1944) shows considerable further enlargement of the heart and aortic shadow.

emergency Cæsarean section, as it was feared that the aneurysm might suddenly rupture into the pericardial sac. She remained in the hospital for 5 days. During this time she complained of attacks of pain over the base of the skull. Other times, pain was present in the neck and over the precordium. The chest pain was accentuated by deep breathing. There were 2 minor exacerbations of pain in the base of the skull and precordium on the 2nd and 3rd days of her stay. These required morphine, which afforded relief. The evening of Feb. 12, 1944, she suddenly went into collapse, became unconscious, was pulseless and the blood pressure was unobtainable. Some minutes after this she became conscious, complained of severe pain at the base of the skull and in the anterior chest, for which she was given morphine ($\frac{1}{6}$ gr., and atropine, $\frac{1}{150}$). Improvement followed, so that the blood pressure returned to the previous level.

During the late afternoon of the 5th hospital day (Feb. 14, 1944) there was a sudden loss of consciousness. The patient became cyanotic and suffered a mild convulsive seizure. Respirations were deep and slow and she died 3 minutes later. A postmortem Cæsarean section was performed and a viable baby obtained which weighed 2 pounds 15 ounces. The baby lived for 3 hours.

Autopsy. The body was that of a normally developed well-nourished young white female. The pertinent pathologic findings were in the heart and aorta.

The pericardial cavity was tense and distended by approximately 750 cc. of liquid and clotted blood. The serosal surfaces of the parietal and visceral pericardium were covered by deposits of fibrin. The heart weighed 390 gm. There was a bicuspid aortic valve which measured 7 cm. in diameter. The cusps were well formed and showed no evidence of thickening. The remainder of the heart was not remarkable. The aorta, at a point 9 cm. above the aortic valve and 0.8 cm. distal to the mouth of the left subclavian artery, narrowed

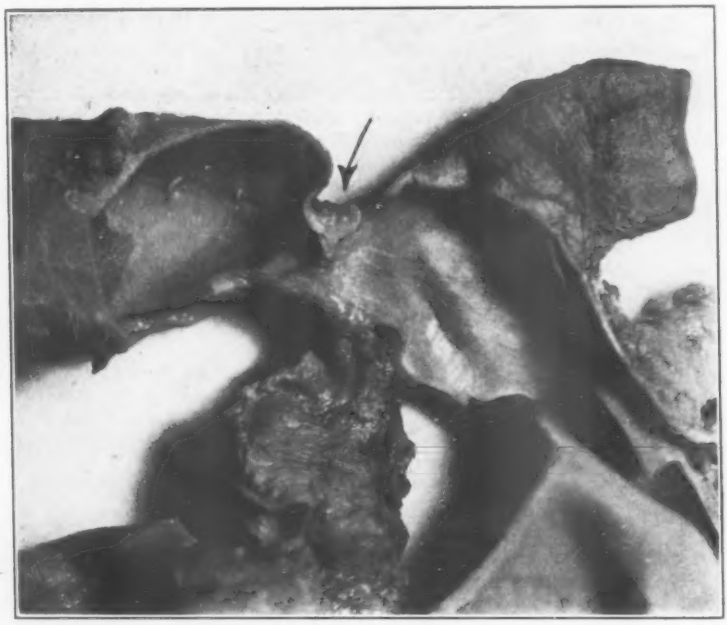

FIG. 3.—Aorta showing point of coarctation. (See arrow.)

abruptly to a diameter of 3 mm. (Fig. 3). This diameter was maintained for a distance of 5 mm. when the aorta abruptly widened to a circumference of 5.2 cm. There was a ragged tear in the aorta which began at a point 1 cm. above the aortic valve and extended up and laterally across the aorta for a distance of 3.5 cm. (Fig. 4). Blood had dissected through the tear and back into the pericardial cavity. Dissection had also extended up the ascending aorta, between layers of the media involving the innominate and right carotid arteries. The lumen of the carotid artery was partially occluded. The aorta distal to the point of narrowing was somewhat smaller but otherwise not remarkable.

Microscopic Examination. Multiple sections of the aorta were taken both proximal and distal to the point of coarctation as well as from the point of rupture. These were fixed in 10% formalin and stained with hematoxylin eosin and Weigert's elastic tissue stains. The intima in all sections was thin

FIG. 4.—Aorta showing point of rupture. (See arrow.)

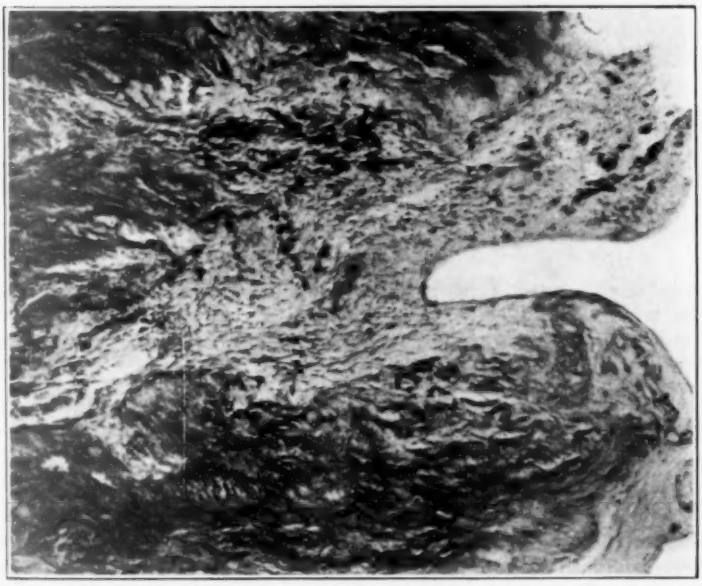

FIG. 5.—The ascending aorta at the point of rupture showing the marked loss of elastic tissue and replacement by scar tissue. (Hematoxylin and eosin, × 97.)

and regular and showed no evidence of atheroma or other changes. The internal elastic lamella was intact and of uniform thickness.

The media in all sections of the aorta proximal to the point of coarctation showed marked changes. There were many areas in which there was loss of both muscle cells and elastic tissue. Elastic tissue stains showed breaks in the continuity of the elastica in these areas. In the sections taken from the ascending arch of the aorta and particularly in those near the point of rupture the loss of elastic tissue was especially severe (Fig. 5). In these areas there were numerous cavities filled by mucoid-like material from which the elastic tissue had completely disappeared (Fig. 6). These cavities were bordered by apparently normal media. In one area, near the point of rupture, approximately a third of the media was devoid of elastic tissue and the defect was replaced by loose fibrous scar tissue which was relatively avascular (Fig. 8).

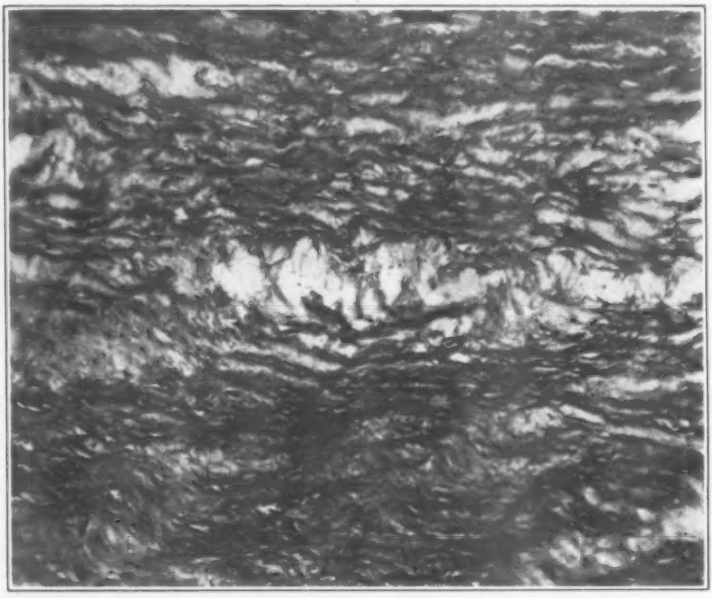

FIG. 6.—The ascending aorta demonstrating the marked cavity formation in the media. (Hematoxylin and eosin, × 125.)

Similar smaller areas were present throughout the sections taken from the aortic arch. No adventital lesions could be demonstrated. It should be noted that no evidence of inflammation was found in any of the sections of aorta studied. No lesions of the media were present in the sections taken from the aorta distal to the point of coarctation.

Sections of the myocardium were not remarkable except for the pericardial surface. Here, there was recent blood clot and the subpericardial space was moderately infiltrated by neutrophils and mononuclear cells.

Postmortem examination of the fetus showed marked pulmonary atelectasis. The heart, aorta and other organs were normal.

Comment on Pathologic Findings. The changes in the media of the aorta proximal to the point of coarctation were similar to those described by Erdheim,[5] Moritz[6] and others and to which the name "Medionecrosis aortæ idiopathica cystica" has been given. This

lesion has not been noted often in coarctation of the aorta. Harrison[7] has reported a case in which this type of medial degeneration was present in the arch of an intact coarcted aorta. Gloggengiesser[8] described a case of coarctation in which dissection was associated with medial necrosis. Abbott and Hamilton,[9] in a review of the literature in 1928, found 33 cases in which there was spontaneous rupture of the ascending aorta and in 13 of these the microscopic examination of the wall of the ascending aorta adjacent to but not involved in the rupture was made. In 1 case, the wall of the aorta was considered to be normal while in all the other aortæ there were marked changes in the media, which were described as consisting of interruption and diminution of the elastica with hyaline and occasionally fatty degeneration. These changes were considered by Abbott and Hamilton to be evidence of inherent weakness of the media. It should be pointed out that all of the cases discussed by Abbott and Hamilton were reported before Erdheim's description of medial necrosis cystica and therefore it is possible that many of these cases would today be considered examples of medial necrosis rather than of developmental defects of the media. Of particular interest in the present case, and in Harrison's case was the fact that the medial lesion was present in the aorta proximal to the point of coarctation and absent in that portion of the aorta distal to the coarctation. In a third unreported case seen by one of us this combination of circumstances was also true.

In a review of dissecting aneurysm in young individuals, Schnitker and Bayer[10] found that there was a high incidence of congenital narrowing of the aorta varying in degree up to coarctation. The large number of young pregnant women in their review led them to speculate concerning the possible relationship between altered lipid metabolism and acute dissection of the aorta. This problem needs further investigation.

Clinical Discussion. Acute dissection of the aorta and coarctation of the aorta are individually not very rare. However, the presence of both occurring in a young pregnant woman is quite uncommon, and only 2 other such cases have been reported. It is of interest that the clinical antemortem diagnosis was not difficult. The onset of sudden severe pain in the throat and the back of the neck which also involved the upper back and left arm directed attention to the possibility of a vascular accident. In the case reported by Katz[4] similar pain in the throat and neck was a prominent feature. The routine examination, which revealed absent femoral and abdominal pulsations, quickly focussed attention on the possibility of coarctation of the aorta. This readily explained the basal systolic murmur and led us to listen to the interscapular region where the same murmur was audible. Furthermore, confirmatory evidence was obtained when a pulsating artery was detected in the left midback, and no blood pressure reading could be made out in the legs. It is of interest that this clinical diagnosis was made even though the Roentgen ray examination first overlooked the changes in the ribs. After the diagnosis of coarctation had been established, the obvious explanation for the symptoms appeared to be

a rupture of the aorta. The palpable thrill in the region of the right carotid artery and the decrease in blood pressure in the right arm indicated that the dissection had extended to partly occlude the right carotid and innominate arteries. As rupture into the pericardial sac is a frequent complication of dissecting aneurysm of the ascending aorta, the final outcome in this case was anticipated.

Summary. A case is reported in which an acute dissection of a coarcted aorta occurred in a young pregnant woman. Death took place abruptly as a result of rupture of the dissection into the pericardium. This is the first instance in which the complete anatomic diagnosis was made antemortem.

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COMBINED ACUTE VASCULAR LESIONS OF BRAIN AND HEART

A CLINICAL-PATHOLOGIC STUDY OF 15 CASES

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THERE has been little mention in medical literature concerning the simultaneous occurrence of acute cardiac infarction and acute cerebrovascular accident. In 1937, Dozzi[2] reviewed 107 autopsies of hemor-

rhage, thrombosis or embolism of the brain. He found that 12 cases (11.2%) had an associated coronary thrombosis. He also stated that among 41 cases of coronary thrombosis, 12 (29%) had an associated cerebral vascular lesion. He gave no details of the pathology, nor did he describe the acuteness or chronicity of the lesions. In 1939, Dozzi[3] reported electrocardiograms taken on 66 cases of hemiplegia. In this group, there was evidence of coronary thrombosis in 8 (12.1%). He commented on the close approximation of the figures in the material from autopsy and of the cases of hemiplegia. Among the 66 cases, 15 came to autopsy, including 4 of the 8 cases diagnosed as coronary thrombosis. The coronary thrombosis was verified in these 4 instances, in 2 of which coronary occlusion was of recent origin and in 2, of remote origin. Meakins and Eakin,[4] in 62 cases of coronary occlusion, found an associated cerebral thrombosis in 6.4%. Among 83 autopsies of coronary thrombosis, Parkinson and Bedford[5] reported 1 case of cerebral embolism. Conner and Holt,[1] in a study of 287 cases of myocardial infarction, found 14 cases (4.9%) with associated cerebral emboli.

The present report is a review of 100 consecutive autopsies performed at City Hospital from 1938 to 1944 in which either an acute myocardial infarction, with or without coronary thrombosis, or an acute cerebral vascular accident was found. In the entire series, there were 15 cases with combined acute vascular lesions of both brain and heart.

Of the 100 cases, 90 were in whites and 10 in negroes. The sexes were equally divided, 50 in each group. The ages ranged from 25 to 88 years, the youngest patient being a white female 25 years old; the oldest, a white female 88 years old. The age distribution in decades was as follows: 20-29, 2; 30-39, 3; 40-49, 13; 50-59, 24; 60-69, 29; 70-79, 20; 80-89, 9. Of the 15 cases with the combined lesions, 9 were in women and 6 in men. It is unusual to find a female predominance in any statistics associated with acute coronary occlusion and particularly so in reference to its complications. Indeed, White[7] states that the male sex is more often affected, "at least to a serious degree," by coronary disease than is the female. Their average age was 65.4 years, the youngest being a male 34 years old, and the oldest, a male and a female, both 82. All the patients were white.

Among the 15 cases with the combined lesions of heart and brain, the cerebral lesions proved to be of various characters. The most frequent lesion found in the brain was cortical petechial hemorrhages, usually of widespread, unilateral distribution. See Figure 1. Massive intracerebral hemorrhage was almost as frequent. There were only 2 cases of extensive encephalomalacia. Of the cardiac lesions, there were 6 cases of acute coronary thrombosis with infarction and 9 instances of extensive acute myocardial infarction without thrombosis. The details of these findings are given in Table 1.

The clinical features in the cases with the combined lesions of brain and heart are of particular interest. The presenting symptomatology was more frequently neurologic in nature. The cardiac symptomatology was less frequent. There were some cases in which symptoms

referable to both organs were present, but usually the neurologic signs were more striking. There were only 2 cases completely lacking in neurologic signs and symptoms. There were 8 cases with complete absence of cardiac complaints. The chief presenting symptoms and signs are given in Table 2.

TABLE 1.—PATHOLOGIC FINDINGS OF HEART AND BRAIN

Brain	Acute coronary thrombosis	Acute myocardial infarction without thrombosis
Small intracerebral hemorrhages	1	1*
Massive intracerebral hemorrhages	0	4
Massive encephalomalacia	2	0
Cortical petechial hemorrhages	2	3
Intracerebral petechial hemorrhages	0	1*
Cortical and intracerebral petechial hemorrhages	1	1

* Both cerebral lesions found in the same patient.

TABLE 2.—PRESENTING SIGNS AND SYMPTOMS

Coma	8
Hemiparesis	1
Hemiplegia	8
Aphonia	2
Chest pain	5
Cardiac decompensation	2
Absent neurologic findings	2
Absent cardiac findings	8

The correct clinical diagnoses of combined lesions of brain and heart were made in only 2 instances. In 2 other cases, they were suspected. In 2 cases, the cardiac infarction was correctly diagnosed and in 7 instances, the correct diagnosis of the cerebral lesion was made. Neither lesion was suspected in 2 cases. That the cerebral lesion was more often correctly diagnosed may be attributed to the fact that the neurologic signs and symptoms were predominant.

The brief histories and pathologic findings of 4 illustrative cases are presented.

Case Abstracts. CASE 1. A 52 year old white male had had previous twinges of precordial pain. On the night of admission, he awoke from sleep, vomited and felt a choking sensation over the upper part of his chest. His breathing became labored and he lost consciousness. Physical examination revealed a comatose, non-cyanotic individual. His heart sounds were good. Blood-pressure: 170/110. His reflexes were normal and equal except for bilateral Babinski signs. An electrocardiogram showed an acute anterior coronary occlusion. Blood sugar: 236 mg. per 100 cc.; blood N.P.N.: 35 mg. per 100 cc. The temperature and pulse rose, the patient went rapidly downhill and he died 24 hours after admission.

AUTOPSY revealed an acute coronary thrombosis of the anterior descending branch of the left coronary artery with myocardial infarction. There was an aneurysmal dilatation of the left ventricle and a rupture of the left ventricle at the junction of the lateral ventricular wall with the aneurysm. There were also cortical and intracerebral petechial hemorrhages of the left frontal and temporal and right frontal and parietal lobes, and of the pons, medulla and the deep portions of the island of Reil (see Fig. 1).

CASE 2. A 71 year old white male had had frequent attacks of cardiac decompensation. Three years ago, there was an attack of loss of speech from which he recovered in 5 months. On admission, he was speechless and stupor-

ous. His face was twisted to the right. The liver was palpable and tender. The heart showed a normal sinus rhythm with no murmurs. Blood pressure: 230/175. The deep reflexes were absent in the right arm and the Babinski sign was positive on the right. Blood sugar: 87 mg. per 100 cc.; blood N.P.N.: 32 mg. per 100 cc. An electrocardiogram revealed disease of the left ventricular muscle. The patient became dysarthric and then anarthric. The pulse and temperature rose, signs of consolidation developed at the right base and the patient died 9 days after admission.

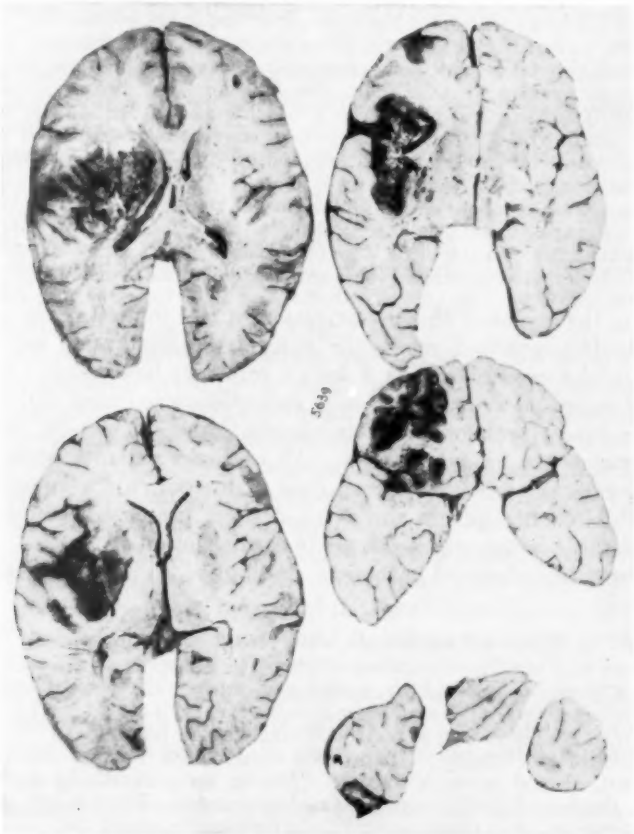

FIG. 1.—Photographs of a brain illustrating extensive petechial cortical hemorrhages involving the frontal lobe, the island of Reil, the occipital lobe and the basal nuclei.

AUTOPSY revealed acute cardiac infarction of the left ventricle without thrombosis. The brain showed cortical atrophy of the right cerebrum and superior gyrus of the left temporal lobe, cerebral arteriosclerosis and acute massive intracerebral hemorrhage of the left basal nuclei, involving the internal capsule.

CASE 3. An 82 year old white female was found lying on the floor, unable to speak or to move her right arm or leg. She had had a similar stroke 14 years ago. On physical examination, the heart was found to have a normal sinus rhythm. There were no murmurs. Blood pressure: 220/100. There were occasional dry râles at the right base. There was a right hemiplegia with a

right facial paralysis. The Babinski sign was positive on the right. The temperature and pulse rose, moist râles developed in the chest, the patient became cyanotic and she expired 3 days after admission.

AUTOPSY revealed an acute cardiac infarction of the left ventricle and the distal portion of the interventricular septum without thrombosis. There was a hemorrhagic area in the left basal ganglion region including the thalamus, the posterior portion of the lenticular nucleus and the posterior limbs of the internal capsule and the external capsule. There was also atrophy of the right parietal-occipital region.

CASE 4. An 82 year old white male fell from a chair, and developed a motor aphasia and paralysis of the right upper and lower extremities. Shortly afterwards, he lost consciousness. He was comatose on admission. Physical examination showed a right facial paralysis. There were bilateral basal râles. The heart was enlarged to the right. No murmurs were heard. Blood pressure: 150/100. There was paralysis of the right arm and leg and the Babinski sign was positive on the right. The patient developed dyspnea and cyanosis with loud coarse râles and a rise in temperature to 103°. He expired 4 days after admission.

AUTOPSY revealed acute cardiac infarction of the apex of the left ventricle without coronary thrombosis and multiple areas of infarction in the wall of the right ventricle. In the brain were found cortical and intracerebral hemorrhages of the frontal and parietal lobes and of the lenticular nucleus.

During the course of this investigation, it was found that in another 5 of the 100 reviewed cases, the clinical manifestations led to the diagnosis of a cerebral accident with a resultant hemiplegia. In each of these cases, an acute myocardial infarction was found and in each case the brain, both on gross examination and on section, failed to reveal any acute vascular lesion. All of these patients were males, their average age was 65.2 years. Four of the patients were comatose, all 5 exhibited hemiplegia and none of them presented symptoms or signs referable in any way to an acute cardiac lesion.

The brief histories and pathologic findings of 2 illustrative cases are presented.

CASE 5. A 68 year old white male, while seated in a chair, suddenly slumped to the floor and developed paralysis of the left leg, arm and face. There was no loss of consciousness but his speech was thick. The patient had had a stroke 5 years before. Physical examination revealed a semistuporous patient with a left hemiplegia and a positive Babinski sign on the left. The heart sounds were of poor quality. There was a regular sinus rhythm. No murmurs were heard. Blood pressure: 135/88. During the patient's 15 days in the hospital, the neurologic findings remained unchanged. For the last 48 hours, he was stuporous, then comatose and had a terminal fever of 103°.

AUTOPSY revealed an acute thrombosis of the anterior descending branch of the left coronary artery with progressive myocardial infarction. On gross examination and on section, the brain revealed 2 well-demarcated areas of softening and atrophy, 1 in the inferior portion of the island of Reil and the other in the posterior portion of the right occipital lobe. Otherwise, the brain was negative.

CASE 6. A 74 year old white male fell twice and developed difficulty in speaking on the day before admission. Physical examination revealed a patient with a left seventh nerve paralysis. The rhythm of the heart was irregular. There were no murmurs. Blood pressure: 150/110. The reflexes were normal and equal. The Babinski sign was negative. On his third hospital day, he was found in coma with signs of a left hemiplegia. The next day he developed diffuse râles through both lung fields. He expired 7 days after admission.

AUTOPSY showed a progressive myocardial infarction without thrombosis. On gross examination, the brain was negative.

Comment. The evidence from these cases indicates that clinical findings alone are not sufficient basis for establishing the co-existence of the two acute lesions. The etiology of the hemiplegia in these cases is an interesting point for speculation. Perhaps the best explanation is the development of a temporary anoxemia of the brain caused by the sudden drop in blood pressure which usually accompanies an acute cardiac infarction. The fact that 4 of the 5 patients were comatose may be cited in support of this theory.

Discussion. It is obvious from the data presented that acute myocardial infarction may be masked by the presence of an associated acute cerebral vascular accident or by neurologic signs having no demonstrable pathologic explanation. It is equally obvious, therefore, that every case with neurologic evidences of a cerebral lesion should also be considered as a case of acute coronary occlusion until proven otherwise. If such an error can occur in one out of every 5 cases, then this caution is certainly warranted. The discovery of an associated acute myocardial infarction will change the treatment and may well alter the prognosis.

In reviewing the cause of death in these 20 cases, it was found that in 11, a major factor in the demise of the patient was an acute broncho- or lobar pneumonia. The pattern for this ultimate termination was seen in the case histories of Patients 2, 3, 4 and 6. The high incidence of this terminal factor raises the pertinent question as to whether the prophylactic use of sulfa drugs should be employed in all cases of cerebral accidents and acute cardiac infarctions.

Summary. 1. A review is presented of 100 consecutive autopsies with either an acute myocardial infarction or an acute cerebral vascular accident in which both the brain and the heart were examined.

2. Fifteen cases (15%) were found to have both acute myocardial infarctions and acute cerebral vascular accidents.

3. Five cases were found to have neurologic signs pointing to a cerebral accident. The brains in all 5 cases were negative on gross examination and on section, whereas acute myocardial infarctions were demonstrated in all of them.

4. It is suggested that in every case with neurologic evidences of an acute cerebral vascular lesion acute cardiac infarction be carefully considered and explored.

5. The suggestion of the use of sulfa drug prophylactically in these cases is raised, in view of the high incidence of terminal lobar and broncho-pneumonia.

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THE RELATIONSHIP BETWEEN CELLS AND PLASMA IN CULTURES OF THE BUFFY COAT FROM HUMAN BLOOD

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Since the recent report by Draper, Ramsey and Dupertuis[2] on variations in behavior of cultured leukocytes from individuals of different constitution types, further observations have been made of the cellular and humoral relationships in such preparations. Previous workers in the field of tissue culture have been faced with the question of whether the cellular component of the explant or the plasma medium is responsible for modifications in the form and migration of outwandered cells. Walton,[5] working with rabbit testicle, thyroid and kidney tissue in various rabbit plasmas, concluded that the plasma alone was responsible for variations in cell growth. It should be noted, however, that Walton's experiments were concerned with fixed tissues of different organs. Carrel[1] believes that monocytes act as delicate indicators of the quality of the serum media in which they may be growing. He points out that changes in the plasma which the monocyte reaction detects may be related to the serum provider's age, state of nutrition, or pathologic condition.

The foregoing remarks bear upon two problems. The first concerns the relative importance of cells and plasma as factors in determining the character of cell morphology and behavior. The second raises the question of the extent to which a given individual's cells exhibit individual specificity. Species specificity of the cells is known to exist and Landsteiner's blood groups point to subspecies specificity in red cells as well. As yet, however, there is little evidence bearing on species specificity in the white cells of the blood. The possibility that some such cellular identity exists, however, receives support from Landsteiner's[3] observation based on precipitin reactions: ". . . in spite of cultivation of chicken tissues in foreign plasma over an extended period there was no loss of species specificity." But, to the question of individual specificity, the work of Loeb[4] on living tissue transplants brings convincing evidence. In line with Loeb's demonstrations, recent findings in this laboratory, based upon observations of human leukocytes incubated in autogenous and homogenous plasmas, point not only to a factor supplied by the plasma component of the culture but also to the positive contribution by the leukocytes as well.

Experimental Procedure. The technique used here for preparing tissue cultures has been described previously.[2] The necessity for washing the cells

in order to free them completely from their own adherent film of autogenous plasma before transplant into foreign plasma is evident.

Two experiments were planned to investigate the part played by plasma and cells in determining the extent and rate of migration as well as individual cell form and conduct. A total of 127 individuals supplied the blood; some of the recovered clinical cases were in good health.

As an early use of this method of investigating specificities in white blood cells, this study did not attempt to identify, in the hematologic sense, the various types of leukocytes in the buffy coat culture. In a previous paper[2] we reported that polymorphonuclears and large mononuclear cells differed greatly in behavior and survival time. These differences were important factors in what we have presumed to be constitutional cell patterns. The small lymphocytes, of all the white cells, have consistently displayed almost no visible change of aspect or special activity.

In an attempt to exclude extraneous factors from influencing the size of the areola we have standardized, as far as possible, the size of the explant, the amount and proportions of the medium, and have drawn the blood at a generally constant time after breakfast in the morning. We also ran a few experiments to determine how much explant size influenced areola size. It turned out that this influence was slight. Apparently during the first 3 hours the cells migrate mainly from the surface layers of the explant.

In the first experiment, blood specimens from 127 individuals (8 normal, the rest representing 19 different diseases) were studied in pairs (88 instances), threes (23), and fours (16). Four cultures were prepared for each pair. One culture for each member of the pair was composed of its own plasma and cells (autogenous) and one of its own cells incubated in its partner's plasma (homogenous). In the groups of threes and fours the same procedure was carried out so that the buffy coat of each blood sample was cultured in its own and in each of its companion plasmas.

TABLE 1.—EFFECTS OF AUTOGENOUS AND HOMOGENOUS PLASMAS UPON 3 DIFFERENT BUFFY COATS

Cells	Plasma	Clinical diagnosis and constitutional type	Blood type	Areola		Activity of cells	Cellular morphology
				Width	Density		
S	s	Tuberculosis linear, muscular type	A	Nar.	Med.	Extr.	Cells with small thin projections; at 24 hours many broad, long, pale cells (see Fig. 1, 1)
S	r	....	..	Nar.	Med.	Mod.	Many small, round cells, and many large bizarre, pale cells; at 24 hours long, thin cells (see Fig. 1, 2)
S	t	....	..	Nar.	Med.	Mod.	Cells with 1 or 2 blunt pseudopodia; at 24 hours many very long, pale cells (see Fig. 1, 3)
R	r	Myocardial infarction	A	Wide	Thick	Mod.	Majority of cells with numerous small blunt pseudopodia appearing very knobby (see Fig. 1, 4)
R	s	....	..	Wide	Med.	Mod.	Much cell death and many pale, broad cells; occasional long cells becoming very numerous at 24 hours (see Fig. 1, 5)
R	t	....	..	Wide	Med.	Slight	Much cell death and many round cells; at 24 hours clumps of round cells (see Fig. 1, 6)
T	t	Poliomyelitis lat., stocky type	B	Very nar.	Thin	Mod.	Cells with 1 or 2 blunt pseudopodia; at 24 hours many broad, pale cells, only occasional long thin cell
T	r	There were insufficient T cells to complete this cross					
T	s	....	..	Very nar.	Thin	Slight	Much cell death; many round cells; at 24 hours many round and many irregular pale cells

Buffy coat is designated by capital letter. Plasma designated by small letter. Explant, R, S, T. Plasma, r, s, t.

For the second experiment, 42 buffy coats from blood of 42 of the patients were cultured (*a*) in the plasma of an individual who had suffered from infan-

tile paralysis 16 years previously, and (*b*) in its own plasma. In both experiments all the cultures were incubated at 37° C. and were observed at 3 and 24 hour intervals. Areola width and density, individual cell morphology, and the activity of the migrating cells were recorded. (See Tables 1 to 4.) In addition, the red cells of each blood sample were classified according to the Landsteiner method.

TABLE 2.—EFFECT OF AN INTERCHANGE OF LEUKOCYTES AND PLASMA UPON AREOLA SIZE

Cells	Plasma	Clinical diagnosis and constitutional type	Blood type	Areola		Activity of cells	Cellular morphology
				Width	Density		
W	w	Chr. myelo. leukemia	O	Nar.	Med.	Mod.	Very large cells, clumped together and regular in shape
W	x	....	..	Nar.	Med.	Mod.	Very large cells, clumped together and regular in shape
X	x	Infec. mononucleosis	O	Nar.	Med.	Mod.	Many small round cells; many cells with 1 or 2 blunt pseudopodia
X	w	....	..	Very wide	Very thick	Mod.	Many small round cells; many cells with 1 or 2 blunt pseudopodia

Buffy coat designated by capital letters. Plasma designated by small letters. Explant, W, X. Plasma, w, x.

TABLE 3.—AN INSTANCE OF CROSSED LEUKOCYTES AND PLASMAS SHOWING NO CHANGES

Cells	Plasma	Clinical diagnosis and constitutional type	Blood type	Areola		Activity of cells	Cellular morphology
				Width	Density		
Y	y	Diabetes mellitus	B	Med.	Med.	Mod.	Many cells; many long cells; at 24 hours no long cells
Y	z	....	..	Med.	Med.	Mod.	Many cells; many long cells; at 24 hours no long cells
Z	z	Hypertension, contact dermatitis	O	Very wide	Med.	Mod.	Many pale, broad, angular cells; some cells with very sharp projections
Z	y	....	..	Very wide	Med.	Mod.	Many pale, broad, angular cells; some cells with very sharp projections

Buffy coat designated by capital letters. Plasma designated by small letters. Explant, Y, Z. Plasma, y, z.

TABLE 4.—THE EFFECT OF ONE PLASMA (T) UPON THE LEUKOCYTES OF 3 DIFFERENT INDIVIDUALS

Cells	Plasma	Clinical diagnosis and constitutional type	Blood type	Areola		Activity of cells	Cellular morphology
				Width	Density		
L	l	Mixed type ulcer-G.B.	O	Med.	Thick	Mod.	Round, regular cells; no change at 24 hours
L	t	....	..	Wide	Thick	Extr.	Bizarre cells and much débris; at 24 hours many long, pale cells
C	c	Inf. mononucleosis	O	Nar.	Thin	Slight	Many round cells, with little knobs; at 24 hours many long, pale cells
C	t	....	..	Nar.	Thin	Mod.	A few ghost cells; at 24 hours many round cells but no long, pale cells
J	j	Coronary occlusion	O	Wide	Thin	Extr.	Knobby cells; at 24 hours several long, pale cells and also clumps of round cells
J	t	....				No change	

Buffy coat is designated by capital letter. Plasma designated by small letter. Explant, L, C, J. Plasma, l, c, j, t.

Observations. FIRST SERIES. The varying patterns produced in leukocyte cultures by an interchange of plasmas are illustrated in photomicrographs *1* to *9* of the migrating cells at the periphery of the areola.

Figure 1, *1*, shows the tissue culture pattern produced by the leukocytes, cultured in their own plasma, from an individual with pulmonary tuberculosis. Figure 1, *2* and *3*, illustrates the effects of two different plasmas upon these same leukocytes. An occasional elongated cell may be seen in Figure 1, *2*, whereas, in *3*, the vast majority of cells are elongated and bizarre in shape. Figure 1, *4*, depicts the culture pattern of a patient with coronary disease. The typical knobby cells found in such cultures may be seen in the right hand corners. Figure 1, *5* and *6*, illustrates the effects of two different plasmas upon this case. Very little change can be noted in *5*, but in *6* marked clumping of small round cells appears. The buffy coat of an individual with peptic ulcer is shown in Figure 2, *7*. Figure 2, *8* and *9*, shows the modification of this pattern by homogenous plasmas. It would seem, from the foregoing observations, that the plasma medium was the dominant factor in these reactions. In contradistinction, however, Figure 1, *3* and *6*, and Figure 2, *9*, dispute this conclusion. All 3 cell samples, originating from different human subjects, were planted in the same alien plasma medium. Comparison of the bizarre, elongated cells of Figure 1, *3* (and to a lesser extent, of Figure 2, *9*) with the clumped, sharply outlined, small, round cells of Figure 1, *6*, indicates that the leukocytes also express themselves vigorously as determining factors in the reactions.

Types and variations in cell plasma crosses are revealed in Tables 1 to 4. In certain instances cellular morphology appeared to be greatly influenced by plasma change (see Table 1). This table presents 3 individuals whose buffy coats were each grown in autogenous and homogenous plasmas, but the effect on cell morphology by alien plasma is notable.

On the other hand, Table 2 demonstrates the influence of foreign plasma upon areola size with no changes in cell morphology. Each of the 2 buffy coats, when cultured in their respective plasmas, developed narrow areolas. However, when the leukocytes from an individual with infectious mononucleosis were incubated in the leukemic plasma a very wide and very thick areola was produced. It is further demonstrated by this table that reciprocal action in a given pair does not necessarily occur. Thus, when one buffy coat of a pair is crossed with the other's plasma, there may often be no effect whatsoever. In such a case the culture pattern remains as it originally formed in its own plasma. It does not follow, however, that the buffy coat of the second partner will, when crossed with the first partner's plasma, take on the characteristics of the other's pattern. In still another instance of cell plasma cross (Table 3) no modification in areola size or cellular morphology was observed.

It appears from this first experiment that almost any areola size, and any pattern of cell form and conduct may result from crossing cells and plasmas, and that there is adequate evidence that the cells contribute to the pattern quite as much as the plasma.

SECOND SERIES. The effects of one person's plasma upon the buffy coats of 42 different individuals were studied in the second part of the investigation.

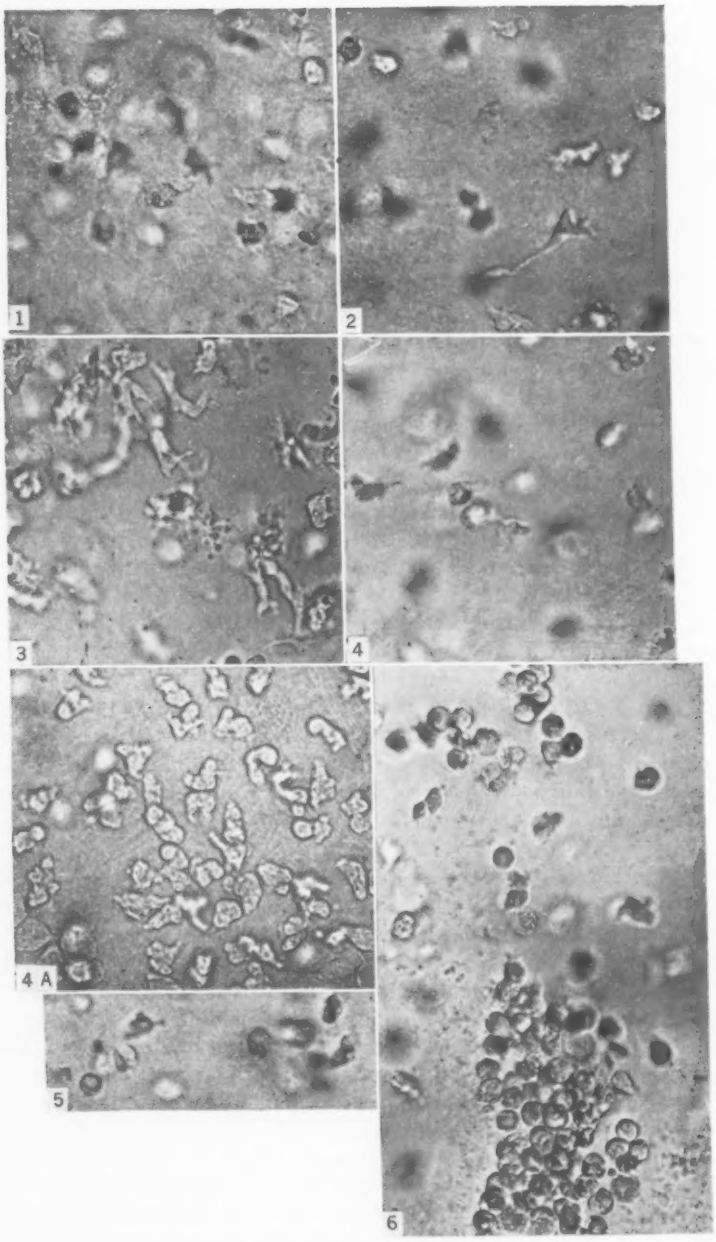

FIG. 1.—*1*, White blood cells and plasma from S, an individual with pulmonary tuberculosis. *2*, White blood cells, S, in plasma, r, from an individual with myocardial infarction. *3*, White blood cells, S, in plasma, t, from an individual who had had poliomyelitis. This plasma was used in several instances (see *6*, *9*, *11*). *4*, White blood cells and plasma from R, an individual with myocardial infarction. Typical knobby cells are seen, one at upper right and the other at the lower left. *4 A*, Another case of coronary occlusion showing the knobby cells to good advantage. *5*, White blood cells from R, in plasma, s, from an individual with pulmonary tuberculosis. *6*, White blood cells, R, in plasma, t, from an individual who had had poliomyelitis. (Magnification, in general, × 480.)

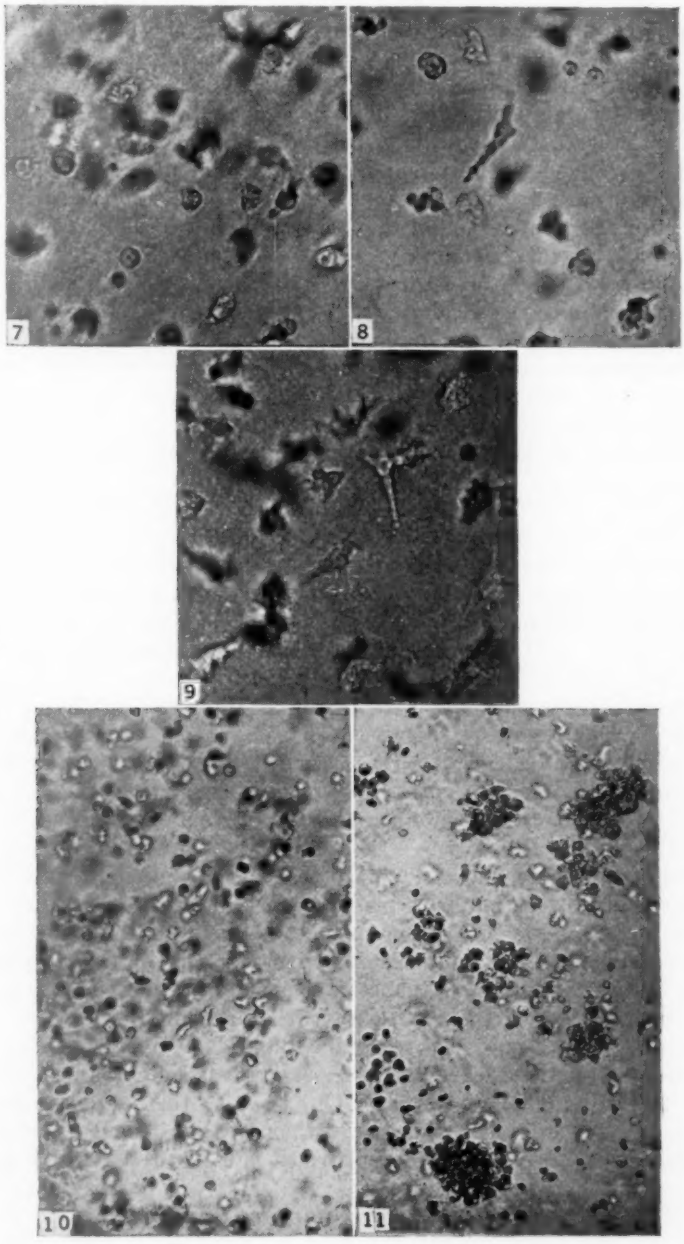

FIG. 2.—*7*, White blood cells and plasma from Oo, an individual with peptic ulcer. *8*, White blood cells, O, in plasma, r, from an individual with myocardial infarction. This plasma was also used in *2* and *8*. *9*, White blood cells, O, in plasma, t. *10*, White blood cells and plasma from an individual with rheumatic fever. *11*, White blood cells, same as *10*, in plasma, t. Note the clumping mentioned on page 744. (Magnification, in general, × 480.)

Explants from each case were prepared and incubated under standardized conditions in their own and in the test plasma from an individual who had been the subject of infantile paralysis. Great variations occurred throughout this series. Of the 42 buffy coat cultures studied, 13 were not affected, 19 were slightly modified, and 10 were greatly changed. In some instances areola size was markedly influenced, in others cell morphology was altered, and in some samples clumping occurred which resembled red cell agglutination. In this connection it might be noted that Carrel[1] described similar clumping appearance in chicken monocytes in pathologic plasma. This phenomenon may be seen in Figure 2, *11*. Figure 2, *10*, shows the same buffy coat in autogenous plasma. At present there is no evidence to explain these white cell clumping reactions or to determine whether the alien plasma or cells contribute most emphatically to the phenomenon. As Figure 2, *11*, demonstrates, it bears a close resemblance to erythrocyte agglutination. In both experiments, however, no correlation between the isoagglutinins of the plasmas and the buffy coat cultures was found.

Discussion. The foregoing paragraphs have described 2 experiments to investigate the rôle played by the cells and plasma in buffy coat cultures of leukocytes: the first, to explore crosses between cells and plasma of different human subjects; the second, to demonstrate the effects of one person's plasma upon the cells of many individuals. Crosses of cells and plasmas between 2 or more persons may result in variations from each one's basic cell plasma culture pattern, and the degree of these changes may extend from nothing (Fig. 1, *4* and *5*) to one of extreme diversity (Fig. 1, *1* and *3*). From the observations here reported we believe that the plasma is not the sole determinant of any given cell culture pattern. A significant part in the complex biologic reactions which produce the various cultures must also be attributed to the leukocytes. At present the relative importance of the two factors is not known. But, if the cells do contribute positively to the combined reaction, with plasma from whatever source, they can only do so because of some inherent factor or factors which they bring to the combination. In our original paper[2] reporting on tissue cultures of the buffy coat of bloods taken from patients whose constitutional types contributed to their development of certain illnesses, it was stated: ". . . in each areola the individual cells may display characters of size, form and behavior quite as specific as those which stamp the individual as a whole." On this basis further observations have made it possible to recognize with increasing frequency and to allocate to its proper source the buffy coat culture presented for diagnosis. Variations in correctness may be explained partly by Loeb's demonstration that not all tissues of an individual exhibit the same specificity, and partly by the fact that cell response in tissue culture is usually less violent than in direct tissue to tissue transplants. However, since the leukocytes are especially active in immunity reactions, it might be expected that they would exhibit a high degree of tissue specificity and sensitiveness to changes in their accustomed media.

If, then, independent specificity exists in each cell, the latter's capacity either to be modified or to be resistant to an alien plasma expresses that individual identity. To anyone who views these cells in the living state, there can be no doubt that the leukocytes from each individual behave in a distinctive way.

Summary. 1. In a first series, the leukocyte buffy coat from each of 127 patients was grown in both autogenous and homogenous plasma samples. The crosses were made at random in pairs, threes, and fours.

2. In this series (No. 1) variations occurred which ran from no apparent change to extensive modifications of areola size and cell behavior.

3. A second series of buffy coats were treated similarly except that the homogenous plasma for 42 cultures came from 1 individual. This person sustained an attack of infantile paralysis 16 years previously.

4. In this second series the variations caused by the single homogenous plasma were as striking as those observed in the first series. As this single plasma did not produce similar effects on all the 42 buffy coats, it was concluded that the plasma medium could not be held solely responsible for the ultimate configuration of the explants.

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CHORIOCARCINOMA OF THE TESTICLE

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During the past 18 months we have encountered 3 new cases of choriocarcinoma of the testicle. In our experience, these tumors in the male have been considerably more frequent than the corresponding tumor in the female. During the course of study of this group of relatively rare tumors, we have made several deductions that seem to us to merit brief discussion.

It is generally agreed by most observers that choriocarcinomas of the testicle are histologically identical with the analogous tumors in the female. It is furthermore agreed that they are almost always

associated with teratomas of the testicle. This feature of appearance of choriocarcinomas with well differentiated teratomatous tissue is well illustrated in two of our cases.

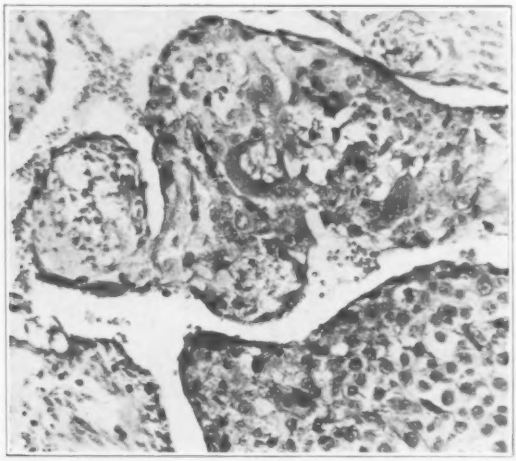

FIG. 1.—Case G4103. Area of choriocarcinoma of testicle with predominance of Langhans cells.

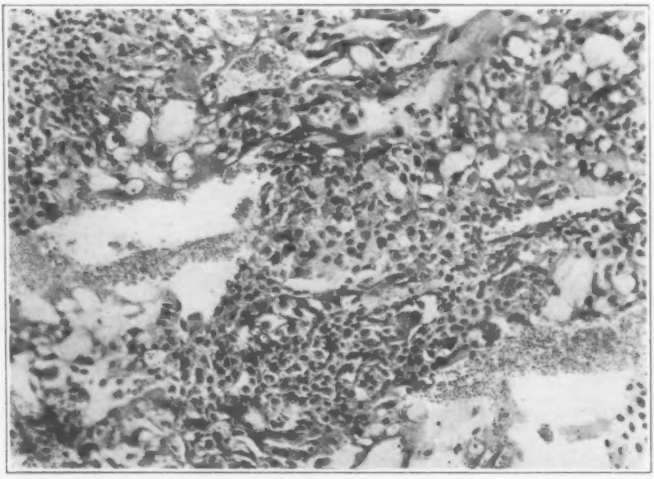

FIG. 2.—Case 56065. Section of the testicular tumor with Langhans and syncytial elements about evenly divided.

Case Abstracts. CASE 1. (No. 50702.) White male, age 55. Known duration of testicular swelling was 3 weeks, during which time there was slight tenderness and rapid increase in size of the mass. No history of trauma or anomalous development was obtained. The mass measured 6 x 5 x 4 cm. Ten days after orchidectomy a test for urinary gonadotropins was strongly positive. The patient expired 3 months following operation with clinical evidence of extensive pulmonary metastases.

Several poorly circumscribed hemorrhagic areas 2 to 3 cm. in diameter were seen on section through the region of the epididymis. Microscopically, the entire tumor, except for masses of typical choriocarcinoma, was obscured by hemorrhage and necrosis.

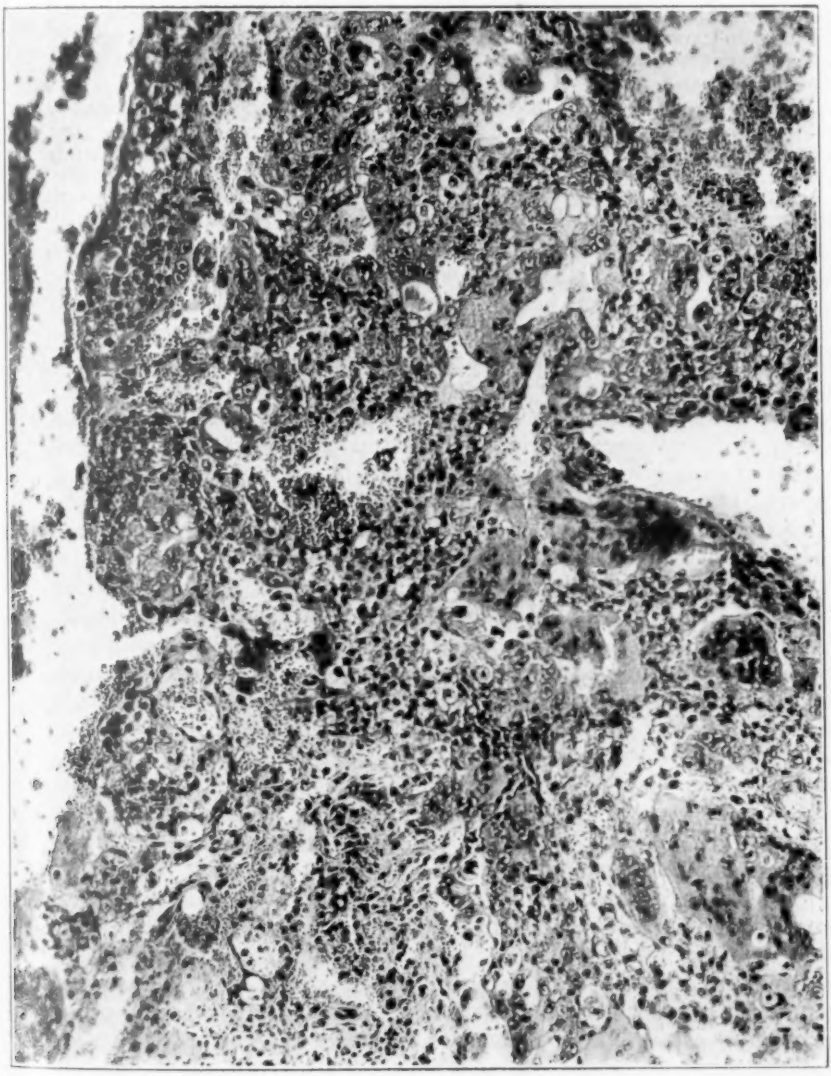

FIG. 3.—Case 50702. In this area of choriocarcinoma of the testicle large syncytial masses are very conspicuous and numerous blood spaces are well illustrated.

CASE 2. (No. G4103.) White male, age 21. The patient noticed a small firm nodule in his left testicle. Two weeks later, the testicle, epididymis and enveloping membranes together with a section of the vas were removed. About 10 days postoperatively, a test for urinary gonadotropins was negative. No history of genital anomaly was obtained. At this writing, about 18 months after operation, he is said to be in excellent health.

A few small irregular hemorrhagic and cystic areas were noted in the region of the epididymis on gross section. Microscopically, epithelium-lined cystic spaces and well-formed gland structures are numerous. Much of the choriocarcinomatous portion is hemorrhagic and necrotic.

CASE 3. (No. 56065.) White male, age 30. This patient experienced a gradual enlargement of his right testicle for 8 to 10 months. On examination there was a testicular mass measuring 6 x 3 x 3.5 cm., and a hydrocele. No history of trauma or congenital anomaly was recorded. A test for urinary gonadotropins was not done and a follow-up report after 12 months is not available.

The gross specimen revealed the usual hemorrhagic and spongy appearance and firmer islets of what appeared to be cartilage. Sections showed a complex mixture of epithelium of various types and arrangements and several islands of cartilage in addition to the trophoblastic elements.

Added to the undeniable histologic similarity of these tumors to the choriocarcinoma of the female there is a functional similarity, in that substances responsible for the positive Aschheim-Zondek test are present in large amounts in the urine of males with this lesion. Hinman and Powell,[8] Freed and Coppock[7] and others have observed that the hormones from placental tissues may be similar functionally to some of those found in the urine in cases of testicular tumor.

Histogenesis of this tumor has occasioned much speculation in the past. Steinert[13] suggests that the teratomas arise from fetal blastomeres or from a fertilized polar body capable of reproducing all fetal layers. Our conception of the blastomere is that any cell of the subdivision of the fertilized ovum up through the morula stage of development and before the blastula stage may be so designated.

Ross[11] observed, in abdominal metastases, what she described as origin of syncytium and Langhans cells from small cubical darkly staining cells which also gave rise to carcinomatous tissue, and were found in blood-vessels, lymphatics, and peripheral sinuses of lymph nodes. She concludes that "formation of chorioepithelioma testis is the expression of a process of specific partial differentiation of these pluripotential cells." According to this author the choriocarcinomatous tissue arises by the metamorphosis of undifferentiated cells which also give rise to teratomatous structures. She felt that in the case reported by her it was not necessary to presuppose even the presence of fetal ectoderm.

Frank[6] suggests that metaplasia of any primitive ectodermal tissue might be responsible for choriocarcinoma. He believed, however, that reported presence of other teratomatous elements in metastases was serious argument against this. Cooke[4] stated that in the cases reported up until the time of his article, 3 had shown structures other than choriocarcinoma in metastases, although these other structures did not show malignant characteristics. This is difficult to explain by any hypothesis. Cooke suggests that a derivative from a germinal blastomere normally present in the testicle may form a teratomatous tumor containing elements of fetal membranes.

If one accepts the histologic and functional similarity of choriocarcinoma of the testicle and its analogue in the female, and since it appears probable that choriocarcinoma of the testicle is always asso-

ciated with teratoma, one might then assume that histogenesis in the male and in the female is the same. It seems probable that the only explanation lies in the assumption that these tumors of the testicle arise from a pluripotential cell with potential capacity similar to ovum and that the origin of choriocarcinoma from fetal ectoderm is not different from the origin of the same tumor in the female. That the germ, be it called blastomere, or simple multipotential cell, from which these tumors develop has potentialities similar to the fertilized ovum, seems evident because of the occurrence of easily recognized elements of two or more germ layers rather regularly in the primary tumors. It is probable that the multipotential cell from which these tumors are derived, is one that is normally present in the testicle. Since there are cells normal to the testicle which appear to fulfill all the criteria required, we believe that the idea of "inclusion" of blastomeres can be deprecated and support offered for another more generally accepted hypothesis, similar to that noted by Ewing,[5] Adams[1] and others, who have indicated spermatogenic cells as the probable origin of teratomatous tumors of testicle. In our opinion, it is entirely reasonable to accept the spermatogonium, the ancestor of the mature sperm in adult testicle, as the multipotential cell capable of giving rise to this group of tumors. It does not seem that there could be any insurmountable objection to the view that the spermatogonium has within itself the capacity to produce many structures since its descendants contribute much to the complete individual in the process of fertilization of another multipotential cell, the ovum.

Several unanswered questions arise, however, before the opinion is fully acceptable. One of these is the question: why does one never see a benign proliferation of trophoblastic tissues in the testicle? One also wonders why chorionic villi or benign hydatidiform mole is not observed in testicular tumors. In regard to this last question Kerwin[9] noted (without reference) that certain unsubstantiated cases of hyatid mole may have occurred.

The question of why choriocarcinoma of the ovary is rarely seen in association with teratoma of the ovary is also a troublesome one. Bettinger[3] has collected 4 cases, Seigmund[12] reported 1, and a few others have been noted. One case, described by Risel,[10] was at first considered a primary choriocarcinoma of the ovary but was finally thought to be secondary to a tiny healed lesion in the fundus of the uterus. That hormone influence may have some effect in choriocarcinoma testis is indicated by age incidence. As Cooke[4] has mentioned in his review of 47 cases, no choriocarcinoma was observed before puberty or after sexual activity had ceased. Steinert also notes the occurrence during sexual maturity. This suggests the possibility that some hormone stimulus may operate or that the cells of origin concerned may tend to proliferate normally with puberty and perhaps atrophy in senile individuals.

Because of the extremely high levels of hormone production and the expectation that the trophoblastic tissues elaborate hormones, it is easy to accept this activity of choriocarcinoma as a real and direct

function of the tumor. One is soon faced, however, with the necessity of explaining the increased levels of similar hormones produced by individuals with testicular tumors of types other than choriocarcinomas. One of the best established of the explanations for this phenomenon had been the assumption that most, if not all, of the testicular tumors were ultimately derived by differentiation from teratomas and that certain elements had so overgrown and displaced the teratomatous portion that tissues of the original teratoma were difficult to find by sectioning. The implication is that even well differentiated teratomas may elaborate hormones. We do not know of any evidence that teratomas in other parts of the body elaborate hormones, except in a rare case where specific endocrine tissues such as adrenal may be present. We wish to support a possible alternative hypothesis that the presence of a lesion of the testicle, even an adult teratoma, may depress testicular function and stimulate excretion of gonadotropic (pituitary) hormones in low titers, which are entirely different from chorionic gonadotropins. In short, it may well be that with the exception of the choriocarcinoma, none of the other testicular tumors, except possibly the very rare Leydig cell tumor, specifically elaborate any hormone whatsoever, and that appearance of various hormones in urine is the result of systemically deranged endocrine balance and/or the presence in the tumor of small amounts of hormone producing tissue which may not be discovered in routine study. A not dissimilar suggestion was expressed by Ross, who noted that a positive Aschheim-Zondek test was possible in tumors other than choriocarcinoma and made the further observation that male breast activity (presumably another evidence of hormone action) may occur with atrophy of testicle, melanoma of skin, and other tumors. As Twombly[14] pointed out, in his experience the chorionic gonadotropin occurs only when active tumor is present, although the castrate type of gonadotropin may exist long after a clinical cure of the tumor. He also notes that he considers the appearance of chorionic gonadotropin in seminomas as a further proof of the teratoid nature of this tumor and suggests that this hormone may be produced by tissue which he calls embryonal adenocarcinoma. Adams[1] actually demonstrated small amounts of what he believed might be trophoblastic tissue in several testicular tumors other than choriocarcinoma. He felt that presence of trophoblastic tissues in varying amounts might account for excretion of gonadotropic hormone in tumors which may appear to be different, but which probably have a common origin.

The chorionic gonadotropin which appears to be the type hormone elaborated by the tumor itself in choriocarcinoma probably should induce atrophy of the testicle because of the high concentration present, and atrophy is sometimes mentioned in patients with choriocarcinomas as well as others of the testicular tumors. Added evidence of endocrine dysfunction such as gynecomastia is often seen in victims of choriocarcinoma. Twombly has raised the question of whether or not there may be some shift in hormone balance which precedes rather than follows and may contribute to the development of testicular

tumors. Deranged testicular function, even prior to the beginning of malignant testicular tumors could stimulate the production of pituitary gonadotropin. This suggestion might explain occurrence of pituitary gonadotropic hormones in some tumors where trophoblastic tissues are not thought to occur.

Conclusions. After histologic study of 3 recent cases of chorio-carcinoma of the testicle and consideration of part of the extensive literature on the subject, we think that there can be little doubt that these tumors arise from primitive cells which have essentially the same capacity as the developing ovum and that the malignant trophoblastic elements of these tumors are derived from ectoderm in the same way as the comparable tissue in ordinary pregnancy. It seems to us that the cells from which these tumors arise are multipotential sex cells normally present in the adult testicle. These cells are probably spermatogonia.

The differentiated elements of the teratoma in testicular tumors are probably not responsible for any hormone production which may be observed, and it is unlikely that any of the testicular tumors with the exception of the choriocarcinoma elaborate any hormone of themselves. In our opinion the finding of gonadotropic hormones in these other tumors suggests either undisclosed trophoblastic tissue or a systemic endocrine dysfunction which, as Twombly mentions, may have preceded the occurrence of the tumor.

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HYDROMETROCOLPOS IN INFANCY—A CAUSE OF URINARY RETENTION, INTESTINAL OBSTRUCTION AND EDEMA OF THE LOWER EXTREMITIES

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Abdominal tumors in female infants are not everyday occurrences in the practice of a physician, but when one meets with a huge cystic mass which can be cured by a simple surgical procedure after definite

diagnostic measures have been employed, and without laparotomy, one should be prepared for such a situation. If the condition is undiagnosed or misunderstood, laparotomy, with its attendant dangers in a young infant, may be unnecessarily employed.

Hydrometrocolpos in infancy was described in 1904 by Commandeur[1] who reported 1 case of his own and reviewed the literature in which 9 other cases were reported. The American literature, however, remained silent and such recent pediatric works as Brennemann's "Practice of Pediatrics,"[2] Schauffler's "Pediatric Gynecology,"[3] and Griffith and Mitchell's "Textbook of Pediatrics,"[4] fail to mention the occurrence of such a complication of a closed vagina before the onset of menstruation. It is briefly discussed in "Therapeutics of Infancy and Childhood"[5] as producing tremendous cystic tumors and is included in the bibliography of the article on Malformations of the Female Genital Organs in Holt's "Diseases of Infancy and Childhood."[6]

In 1940, Mahoney and Chamberlin[7] of Boston thoroughly described the combination of factors leading to such abdominal masses. They reviewed the literature and reported 3 cases of their own and 1 described to them by Dr. Camille Kereszturi of New York. One of their patients had other congenital deformities incompatible with life, another was misdiagnosed and resulted in a panhysterectomy, and a third was diagnosed correctly with the aid of injection of 20 cc. of diodrast followed by Roentgen ray studies. A cystogram showed a bladder compressed from above and behind and pushed forward This child, 2 days after birth, presented a large, tense, round, lower abdominal tumor, reaching to above the umbilicus. A bulge at the vagina was thought to be a rectocele but later was shown to be the protruding cyst wall which bulged further when the baby cried. The hymen was not found, but a probe could be passed around the bulge to a depth of only 1 cm. The patient was cured by incision of the membrane with drainage of several ounces of turbid fluid. The examining finger could easily be inserted full length into the vagina but the markedly dilated wall contracted and gained tone almost immediately. The post-operative course was uneventful.

Kereszturi's patient was a 2 month old girl with diarrhea of 6 weeks' duration and a bout of urinary retention a week before admission to the hospital, July 8, 1937. On admission, after a day of fever, the temperature was 104° (R) and there was a cystic mass extending from the pubis to the umbilicus. A smooth mass protruded between the labia. There was urinary tract infection, and an intravenous urogram showed marked dilatation of the ureters and hydronephrosis. After 1 week, an exploratory laparotomy revealed a cystic mass behind the bladder, pushing the bladder and uterus upward. Pressure on the uterus caused the labial membrane to bulge. This membrane was incised and 2 ounces of milky fluid were released. The pelvic mass disappeared, the urinary tract became normal, and the patient was discharged well on August 26th, 7 weeks after admission. Kereszturi reported this case separately[8] and it appeared in print before the report of Mahoney and Chamberlin.

Because of these reports, Rosenblatt and Woolley were enabled to treat a case successfully, and they described the details in a brief case report in *Annals of Surgery* in 1943.[9] Their patient had a markedly dilated bladder which could be emptied by catheterization. The entire situation was cured by mere incision of the bulging vaginal membrane after Roentgen ray demonstration of the nature of the mass, following withdrawal of some of the fluid and injection of diodrast into the "cyst."

In addition to these reports of cases in infancy, there are 2 recent reports in the literature of similar cases in young girls just before the onset of the first menstruation. In Bowen's case,[10] a 12 year old "identical" twin whose twin sister had an open hymen was found to have an imperforate hymen and a symmetrical mass extending from the pelvis to the umbilicus. Rectally, a smooth walled cyst was felt in the midline. There was a pink spherical protrusion between the labia. The urine was normal, WBC 10,000, polys 80%. An incision into the hymen brought, instead of the expected blood, about 2 quarts of milky chyle-like fluid. The first menstruation appeared 5 months later, almost 3 months after the normal twin had first menstruated. This case brings up the question of whether or not some of the cases of hematocolpos with imperforate hymen might not be similar cases of hydrocolpos later made bloody by the first few menstrual bleedings. Tompkins reviewed 113 cases of imperforate hymen with hematocolpos in the literature and added 5 of his own[11] though Kereszturi found only a few to mention in her report. These cases are undoubtedly much commoner than those with non-bloody fluid, and one wonders why the latter are not oftener encountered. The other case of hydrometrocolpos in a premenstrual girl appeared in the German literature in 1941.[12] A 14 year old girl complained of abdominal pain and backache of 6 weeks' duration. The abdomen had become larger in the preceding 3 weeks. The hymen was imperforate. It was punctured and 50 cc. of cloudy "serous" fluid were withdrawn. A laparotomy was then performed and 2200 cc. of the same type of fluid were obtained by puncture of a large cyst-like structure which arose from the pelvis. Both fluids proved sterile when cultured and no acid-fast organisms grew out on the special culture. The fluid contained a moderate number of leukocytes but no epithelial cells. In spite of hormone therapy, the patient continued amenorrheic after operation although she was well otherwise.

Hydrometrocolpos has also been reported in a woman of 72 years with vaginal stenosis.[13] The presenting symptoms were inability to void and intestinal obstruction. The cause was undetermined after careful study of sections of the removed uterus and vagina, but "senile vaginitis" was offered as a possible etiology of the vaginal obstructions.

This tendency of the greatly distended vagina to displace the bladder upwards and to cause urinary obstruction is well illustrated by our own case.

Case Abstract. F. G., a 7 week old girl, developed swelling of the feet and a purplish discoloration of the lower extremities. This appeared rather sud-

denly during the course of a day in which only 2 slightly wet diapers followed after the baby awoke in the morning with a dry diaper. During the preceding 3 weeks, the mother had noted considerable straining as if the infant were trying to expel a stool at each feeding and that the stools had become ribbon-like in form. The day before, a few blood flecks had appeared in the stool. Many changes of formula had been ordered by the attending physician in order to relieve the difficulty. Two physicians saw the patient during the day of her scanty urinary output. The first ascribed her trouble to constipation and the second suspected intussusception because of the presence of a mass in the lower abdomen and the blood flecks in the stool.

When the infant was first seen by the author, there was obvious pitting edema of both lower extremities, which were purplish in color. This edema and discoloration extended upwards over the lower abdomen about half way to the umbilicus. There was a large cystic mass extending upwards from the pubis and apparently slightly more towards the right side and reaching to 2 cm. above the umbilicus. In addition, there was a peculiar bulge at the vulva, cystic in appearance, pointing anteriorly, somewhat resembling a rectocele with distended viscus pushing into it. There was no visible urethral meatus but catheterization was attempted in order to rule out a distended bladder as the cause of the abdominal "tumor". A small metal catheter was inserted blindly anterior to the vulvar bulge and it entered the urethra easily. A small spurt of clear urine appeared but no more could be obtained even with pressure on the abdominal mass. Rectal palpation revealed a bulging cystic mass anterior to the rectum. In view of the seemingly empty bladder, the abdominal mass was thought to be a cyst or a bladder diverticulum. The swelling and discoloration of the skin of the lower abdomen and lower extremities were interpreted as being due to pressure by the mass on the pelvic veins. It was felt that needle puncture of the vulvar bulge was somewhat risky because there seemed to be a hollow viscus behind it.

Hospitalization and laparotomy seemed to be the most conservative measures. The surgical consultant agreed that an abdominal exploration was indicated and he promptly performed a laparotomy under open ether anesthesia. In spite of the failure of catheterization to obtain more than a few cc. of urine, the large mass proved to be urinary bladder, tremendously distended. A catheter was again inserted into the urethra and no urine flowed until very great direct pressure was exerted on the distended bladder. When the bladder was partly emptied, a second mass appeared behind it. This was recognized as distended uterus and vagina and then only was the true nature of the difficulty recognized. Pressure on this mass, which was only about 5 cm. in diameter, caused an increased tension in the vulvar bulge which was then incised externally. A considerable amount (not measured) of a thin, slightly milky fluid escaped, and the mass collapsed, allowing easy emptying of the rest of the urine from the bladder. The fluid contained some white blood cells but the culture was sterile. Urine obtained the day after operation contained no leukocytes and only an occasional RBC. The baby survived the operation and was doing well until the operative wound disrupted a week later. The eviscerated intestine was replaced with difficulty. A fecal fistula later developed and death followed an operation to relieve an apparent obstruction 34 days after the first operation.

Supportive therapy included many intravenous injections of plasma and blood. Sulfadiazine was followed by a morbilliform eruption, but sulfasuxidine was well tolerated when it was used after the development of the fecal fistula.

Comment. While this case can be listed as an operative mortality, it can safely be said that "error in judgment" played a part. The laparotomy could have been avoided if the failure of the bladder to empty when catheterized had not thrown everyone off the proper diagnostic track. This very fact prompted publication of this paper in an effort to acquaint a wider group of physicians with a condition

which has been generally neglected by the text books on pediatrics and gynecology. Mahoney and Chamberlin[7] go into some detail in attempting to explain the development of the type of fluid present in these cases. It is their feeling, backed by some embryologic data,[16] that there is present an imperforate vagina similar to an imperforate rectum or anus, entirely apart from and above the hymen. One of their cases and that reported by Cranwell,[14] were autopsied and showed the atresia to be above the normal location of the hymen. Bonnet's case[15] also had a normal hymen with a vaginal occlusive membrane above. Cranwell[14] quotes Pazzi as saying that the true pathology in most cases where a thin membrane closes the vagina is not imperforate hymen but failure of perforation of the vagina.

During the first 2 weeks of life, there is marked activity of the cervical glands and the vaginal epithelium resembles the adult type, due to circulating estrogen derived from the mother.[17] Along with these changes, one occasionally finds slight vaginal bleeding in the newborn and, rather regularly, enlargement of the breasts. However, the cervical glands become less active and the vaginal epithelium becomes less keratinized after 2 weeks of age. Thus, there would have to be abnormal activity of the cervical or uterine glands to produce so large an amount of fluid as is found in the older children with hydrometrocolpos. Possibly, the two factors must be present together to produce the condition we are discussing—both obstruction of the vaginal orifice and an unusually large amount of circulating estrogenic hormones. It would be interesting to note if these patients presented unusual breast enlargement after birth.

The Italian literature[18] contains references to the experimental production of hydrometra in animals. The fluid in some of the cases in infants has been reported to contain "glucose."[1] Although Dobszay[17] reported finding no glycogen in the vaginal epithelium of children and older infants, it is regularly present in that of adults.

Summary and Conclusions. The literature relating to hydrometrocolpos is reviewed and a new case is reported. This case presents a new feature, *viz.*, edema and cyanosis of the lower extremities due to pressure on the pelvic vessels.

There is evidence that imperforate hymen is not the cause of the vaginal closure in these cases, but that failure of perforation of the vagina due to arrested embryologic development, such as one finds in imperforate anus, occurs. The peculiar direction of the vaginal bulge in this case supports such a probability.

The condition is recognized in the newborn if the vagina and uterus are sufficiently distended to cause pressure on the bladder and urinary retention. Otherwise, the condition might not be recognized until just before the menarche when there would again be increased activity of the cervical and uterine glands.

The large accumulations of bloody material in some cases of hematometrocolpos after only one or two periods of abdominal cramps might represent cases of preëxisting hydrometrocolpos into which the first menstrual blood has flowed.

Patients with hydrometrocolpos should not be subjected to laparotomy, as simple incision of the vaginal membrane entirely relieves the condition. Preliminary aspiration by needle of some of the cyst fluid and injection into the cyst of 20 cc. of diodrast followed by AP and lateral Roentgen ray views (as suggested by Mahoney and Chamberlin) will clearly establish the diagnosis in doubtful cases.

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THE USE OF PENICILLINASE IN CULTURES OF BODY FLUIDS OBTAINED FROM PATIENTS UNDER TREATMENT WITH PENICILLIN*

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Since Abraham and Chain[1] first prepared from *Escherichia coli* a substance which inhibited the action of penicillin on bacteria and which they named penicillinase, many other observers have obtained substances with similar properties from various organisms.[2,4,7,8] It has been suggested that penicillinase might be used in culture media when cultures are obtained from a patient under treatment with penicillin. If sufficient penicillinase were present in the culture medium to inhibit the action of the penicillin contained in the patient's body fluids, then any organisms present should grow without interference.

With this purpose in mind, we investigated the effect of ordinary blood culture medium upon penicillinase.† We found that, when

* Miss Ruth Mayer and Miss C. Barbara O'Neil rendered technical assistance.
† Penicillinase was supplied by Dr. Harold J. White of the American Cyanamid Co., and by Dr. Charles E. Dutchess of Schenley Laboratories, Inc.

penicillinase was added to veal-infusion broth, and kept at incubator, room, or refrigerator temperature, the penicillinase did not diminish in potency over the course of 4 weeks. Further studies showed that penicillinase, in the concentrations necessary to inhibit the action of the penicillin present in body fluids, did not in itself interfere with the growth of bacteria.

Our next problem was to find the relative rate at which penicillin loses its potency when incubated in broth, alone and with penicillinase. In order to determine this, we added penicillin, in sufficient quantity to make a concentration of 1.25 units per cc., to a flask containing 40 cc. of veal-infusion broth, such as we use routinely for taking blood

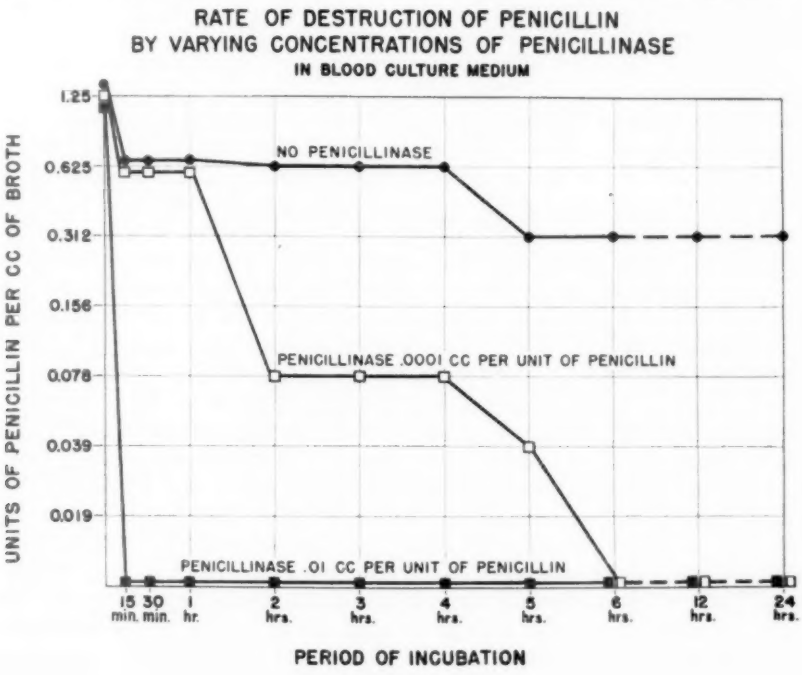

FIG. 1

cultures. This was incubated for 24 hours, along with other flasks containing the same ingredients plus varying amounts of penicillinase. Samples from each flask were removed at frequent intervals and their penicillin content determined immediately by the method of Rammelkamp.[6] Figure 1 shows the result obtained in a typical experiment. In the flask containing no penicillinase, there was only slight diminution in the concentration of the penicillin over the course of 24 hours, while in the flask containing 0.01 cc. of penicillinase per unit of penicillin, no penicillin was detectable after 15 minutes of incubation, when the first sample was taken. When only 0.0001 cc. of penicillinase was used per unit of penicillin, penicillin could still be detected for the first 5 hours, in gradually decreasing concentrations, but not after that time.

TABLE 1.—COMPARATIVE RESULTS OBTAINED, WITH AND WITHOUT THE USE OF PENICILLINASE, IN CULTURES FROM PATIENTS UNDER TREATMENT WITH PENICILLIN

Disease	Etiologic organism	No. of patients	Material cultured	Initial positive culture followed by cultures				
				Positive with or without penicillinase	Negative with or without penicillinase	Negative without penicillinase, positive with penicillinase	Inhibited without penicillinase, positive with penicillinase	Inhibited without penicillinase, negative with penicillinase
Endocarditis	*Strep. viridans*	6	Blood	8	63	2	4	1
Endocarditis	*S. albus*	1	Blood	0	0	6	0	0
Endocarditis	*S. aureus*	1	Blood	0	10	0	0	0
Bacteremia	*S. aureus*	1	Blood	1	10	0	2	0
Meningitis	Pneumococci—Types 2, 6, 12, 31	5	Spinal fluid	1	23	3	0	0
Meningitis	Pneumococcus—Type 31	1	Blood	1	2	0	0	0
Pneumonia	Pneumococci—Types 4, 8, 12, 12	4	Blood	0	5	0	0	0
Empyema	*S. aureus*	1	Chest fluid	0	4	0	0	0
Empyema	*Pneumococci*—Types 1, 2, 4	3	Chest fluid	0	8	3	0	0
Arthritis	*Strep. hemolyticus*	1	Joint fluid	0	2	0	2	0
Arthritis	*S. aureus*	1	Joint fluid	0	3	0	1	0
Pyelitis	*S. aureus*	1	Urine	8	0	0	13	0
	All patients:	26		19	130	14	22	1
				149 (80%)		36 (20%)		

From this and similar experiments we found that penicillin in culture medium, unaccompanied by penicillinase, remained active for 24 hours or longer, and thus inhibited growth of sensitive bacteria during that time. When a sufficient amount of penicillinase was added, it inactivated a therapeutic concentration of penicillin within 15 minutes or less. Insufficient quantities of penicillinase produced no inactivation of penicillin at all, while intermediate amounts of penicillinase produced partial inactivation at first, followed by complete inactivation after variable lengths of time.

We have used penicillinase in veal-infusion broth for culturing body fluids from patients receiving penicillin for various diseases. In each instance a parallel culture was made, using the same medium without penicillinase. In Table 1 are shown the results obtained in 26 patients whose cultures were positive before penicillin therapy was begun. Among the 186 cultures taken on these patients while penicillin was being administered, the results of the cultures taken with penicillinase confirmed the results obtained in those taken without penicillinase in 149 instances (80%). In 19 of these there was growth in both media, and in 130 there was no growth in either. This large number of negative cultures is accounted for by the fact that we continued to take parallel cultures, with and without penicillinase, on several patients long after all clinical evidence of infection had subsided.

In 36 (20%) of the cultures obtained, growth was poor or absent in the medium which lacked penicillinase, while organisms grew well in the parallel culture containing penicillinase. In 14 instances growth was excellent in the penicillinase medium and absent in the other, while in 22 instances growth was excellent in the penicillinase medium and inhibited in the medium lacking penicillinase. This "inhibition" of growth by the penicillin present in the body fluid was manifested in one of two ways: first, by a slowing of growth so that organisms could not be detected until 48 or 72 hours had elapsed, instead of within 24 hours, as had been true before penicillin was administered; or, secondly, by the fact that the bacteria grew sparsely in the fluid medium and not at all when transplanted to blood agar plates.

In only one instance was growth absent in the medium containing penicillinase and present, although the organisms grew sparsely, in the penicillinase-absent medium.

If these results are applied to the number of patients examined rather than to the number of individual cultures taken, the effect of penicillinase is even more striking. There were 26 patients in the group. In 14 (54%) of these, the cultures taken with penicillinase confirmed those taken without penicillinase in every instance. In the case of 8 patients (31%), one or more cultures taken with penicillinase were positive, while cultures taken at the same time without penicillinase were negative. Cultures taken on 4 patients (15%) showed excellent growth in the medium containing penicillinase, while those taken at the same time without penicillinase showed sparse or delayed growth.

Thus in 46% of the patients on whom cultures were taken, the

presence of penicillinase in the medium gave information which was not obtainable or which was delayed or doubtful when the culture was taken without the benefit of penicillinase. Usually, the cultures in which a discrepancy was observed between those taken with and those taken without penicillinase, were the first ones obtained after penicillin therapy was started. We were able to culture the blood from 4 patients with endocarditis and from 1 patient with bacteremia at frequent intervals after therapy with penicillin was begun. Cultures were taken every hour for 6 hours, then at 12 and 24 hours and twice daily for several days therafter. The results are shown in Table 2.

TABLE 2.—TIME REQUIRED BY PENICILLIN ADMINISTERED THERAPEUTICALLY TO INHIBIT OR PREVENT THE GROWTH OF BACTERIA IN THE BLOOD IN RELATION TO THE PRESENCE OR ABSENCE OF PENICILLINASE IN THE CULTURE MEDIUM

			Time after beginning of penicillin treatment before the penicillin			
			Inhibited growth		Completely prevented growth	
Patient	Disease	Etiologic organism	In medium not containing penicillinase (hrs.)	In medium containing penicillinase (hrs.)	In medium not containing penicillinase (hrs.)	In medium containing penicillinase (hrs.)
R. L.	Endocarditis	*Strep. viridans*	1	3	9	9
S. T.	Endocarditis	*Strep. viridans*	1	4	4	5
L. P.	Endocarditis	*Strep. viridans*	6	30	12	54
J. P.	Endocarditis	*S. albus*	..	1	1	*
S. T.	Bacteremia	*S. aureus*	1	4	6	96

* Not prevented. Growth was complete in each of 6 cultures taken hourly. Patient died 3 hours later.

In 3 patients with *Streptococcus viridans* endocarditis, the cultures taken 9, 5 and 54 hours, respectively, after the initiation of penicillin treatment were the first ones to show no growth in the penicillinase-containing medium. In the parallel set of cultures taken without penicillinase, the penicillin present inhibited the bacteria in such a way that the first negative cultures were obtained at 9, 4 and 12 hours, respectively. Likewise, inhibition of growth was apparent sooner in the cultures taken without penicillinase than in the ones containing penicillinase. All 3 of these patients have made what appears to be a clinical recovery from their endocarditis as a result of penicillin treatment.

In the case of the patient with *Staphylococcus albus* endocarditis, there was no growth in the plain blood culture, but the organisms grew profusely in all of the cultures containing penicillinase, which were taken hourly for 6 hours. Further cultures could not be obtained, as the patient died a short time thereafter.

In the case of the patient with *S. aureus* bacteremia (following an operation for fusion of vertebræ), growth was inhibited within 4 hours and completely prevented within 96 hours after the initiation of treatment. In the parallel cultures without penicillinase, these phenomena took place in the cultures obtained 1 and 6 hours, respectively, after penicillin therapy was begun. This patient recovered from his staphylococcic infection.

It is evident that when penicillin is effective against the organism causing endocarditis or bacteremia, the drug clears the blood stream within a few hours to a few days, and that the rate at which the blood is cleared of bacteria cannot be determined correctly unless penicillinase is used in the culture medium.

Cultures were taken on patients with empyema, meningitis and pneumonia at intervals of 24 to 48 hours after the beginning of penicillin treatment. In the 2 cases of pneumococcic empyema in which cultures of the chest fluid remained positive after the beginning of penicillin treatment, pneumococci were grown from the fluid taken as late as 24 and 72 hours, respectively, after penicillin therapy had been started, while no positive cultures were obtained in the media lacking penicillinase.

Two patients with pneumococcic meningitis continued to show positive cerebrospinal fluid cultures after the beginning of penicillin therapy, in one case for 2 days and in the other for 3 days after treatment had been started. The organisms were cultivated only in the medium containing penicillinase, the cultures in the medium without penicillinase being consistently negative after penicillin was administered.

Discussion. When patients are under treatment with the sulfonamides, it has long been the common practice to include para-aminobenzoic acid in the medium used for obtaining cultures from their body fluids. It seems likely that a substance which acts similarly to inhibit penicillin should serve the same purpose when cultures are taken from patients receiving that antibiotic. Numerous investigators have shown that penicillinase possesses such an action, and Harper[3] has used it successfully in culturing surface wounds while they were being treated with local applications of penicillin. We have found that penicillinase can be used to inhibit the action of penicillin in liquid media, and that this method sometimes results in obtaining a positive culture of blood or other body fluid from a patient under treatment with penicillin while the cultures taken at the same time without the use of penicillinase showed no growth, or delayed or inhibited growth.

In a number of cultures the organisms did not grow, regardless of whether penicillinase was used. This was undoubtedly due to the rapidity with which therapeutic doses of penicillin cleared the blood stream and body fluids of susceptible bacteria. In 3 cases of *Streptococcus viridans* endocarditis, for instance, the blood was apparently free of organisms in from 5 to 54 hours after penicillin treatment was started. The important consideration is that one cannot be sure that a particular body fluid has been rendered bacteria-free unless penicillinase is used in the culture medium. We feel, therefore, that it is desirable to use it routinely when cultures are to be taken from patients receiving penicillin.

McQuarrie and Liebmann[5] have devised a method of measuring penicillinase in units. One unit is "that amount of enzyme which, in 11 ml. of pH 7.0 solution containing 50 Oxford units of penicillin,

will destroy in 1 hour at 37° C. an amount of penicillin equal to 57.5% of the penicillin recovered in the control." Recently we have used penicillinase standardized by this method. We recommend that 1 unit of penicillinase be added for each cc. of blood or other body fluid which is to be cultured, except in the case of urine, where 100 units of penicillinase should be used for each cc. of urine.

Summary and Conclusions. 1. Penicillinase does not lose its ability to neutralize penicillin when both substances are added to veal-infusion broth and kept at incubator, room or refrigerator temperature for 4 weeks. In the concentrations in which it is used for this purpose, penicillinase has no inhibitory effect upon the growth of bacteria.

2. Among 26 patients from whom parallel cultures were taken, with and without penicillinase, the presence of penicillinase in the culture medium gave information in 12 patients which was not obtainable or which was delayed or doubtful when the culture was taken without benefit of penicillinase.

3. Among 186 specimens of body fluids obtained from patients under treatment with penicillin, cultured in parallel with and without penicillinase in the culture medium, 36 (20%) showed better growth in the medium containing penicillinase.

4. It is recommended that penicillinase be used routinely in cultures of body fluids obtained from patients under treatment with penicillin.

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INCIDENCE OF RESPIRATORY INFECTIONS FOLLOWING ATTACK BY PRIMARY ATYPICAL PNEUMONIA IS UNCHANGED

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During August and September 1942, a sudden outbreak of primary atypical pneumonia was experienced by the students and staff of the

University of Rochester School of Medicine and Dentistry and the Strong Memorial Hospital. The clinical and epidemiologic features of this sharply circumscribed epidemic have been presented in an earlier paper.[2]

At the time of the institutional outbreak, a number of cases were also observed in the community at large, and cases of atypical pneumonia were reported at a fairly steady rate during the fall and winter of 1942.

In February 1944, an official of the Rochester Board of Education offered the opinion that persons who had atypical pneumonia in 1942 seemed to be relatively free of respiratory infections during the winter of 1943–1944. This official was in a position to observe accurately the state of health of a large number of individuals, and the suggestion that immunity to other respiratory infections might be produced by the agent of atypical pneumonia was therefore given serious consideration. This observation seemed especially significant in view of the fact that the city had just experienced a large epidemic of influenza A.

It occurred to the authors that if the opinion of the official of the Board of Education could be substantiated by controlled study, and if the etiologic agent of atypical pneumonia could be isolated and propagated, this agent might prove to be an effective antigen for immunization against certain common respiratory infections. This line of thought was in keeping with the suggestion of Kneeland and Smetana[1] that atypical pneumonia might actually increase host resistance to bacterial infection. Furthermore, the remote possibility of immunization against at least one other virus by inoculation of the agent (probably a virus) of atypical pneumonia was indirectly supported by the protection against smallpox afforded by the virus of vaccinia.

The object of this paper is to report the incidence of various types of respiratory illnesses among persons who have had atypical pneumonia as compared with those of similar habitat who have not had this disease.

Method of Study. On May 24, 1944, questionnaires were mailed to 150 persons, all of whom were current or former members of the institutional personnel. Replies were received from 114 of these individuals including 9 who had moved to other cities for hospital training or had entered military service. Questionnaires were returned by 33 of the 40 persons who had atypical pneumonia during the August-September outbreak in 1942 and whose illnesses were described in a previous report.[2] In addition, replies were obtained from 6 individuals who had atypical pneumonia subsequent to September 30, 1942. The remaining 75 questionnaires from the control group were returned by those whose names had been selected at random from an alphabetical list published in the annual bulletin of the institution.

Each individual was asked if he had been ill, but not hospitalized, during August or September 1942, and if so, he was asked to state the nature of this illness. In addition each person was asked to give the approximate dates of onset of any of the following illnesses he had had subsequent to September 30, 1942: common cold, sore throat or tonsillitis, bronchitis, influenza, bacterial pneumonia and atypical pneumonia.

All persons questioned were familiar with medical terminology, and in spite

TABLE 1.—INCIDENCE OF RESPIRATORY ILLNESSES AMONG VARIOUS GROUPS OF INSTITUTIONAL PERSONNEL DURING A PERIOD OF 20 MONTHS AFTER AN OUTBREAK OF PRIMARY ATYPICAL PNEUMONIA

Group	Total No. persons in group	No. persons having no respiratory illness	No. persons having 1 or more respiratory illnesses	Number and type of illnesses*						
				Common cold	Sore throat or tonsillitis	Bronchitis	Influenza	Bacterial pneumonia	Atypical pneumonia	Total No. illnesses
A. Persons having atypical pneumonia in Aug. or Sept. 1942	33	2	31	88	14	15	5	1	0	123
B. Persons having atypical pneumonia subsequent to Sept. 30, 1942†	6	2	4	11	0	1	1	1	0	14
C. Persons having other respiratory illnesses during Aug. or Sept. 1942	9	0	9	30	5	6	3	0	0	44
D. Persons having no respiratory illness during Aug. or Sept. 1942 and no atypical pneumonia at any time	66	3	63	191	12	15	14	0	0	232
Total:	114	7	107	320	31	37	23	2	0	413
A. Av. number of illnesses per person year for all persons under observation‡	...	...	...	1 60	0 25	0 28	0 09	0 02	...	2 24
B.	...	...	...	1 83	...	0 17	0 17	0 17	...	2 33
C.	...	...	...	2 00	0 35	0 40	0 20	...	...	2 93
D.	...	...	...	1 79	0 11	0 14	0 13	...	...	2 17

* These groups are, insofar as possible, mutually exclusive.

† The date of onset of atypical pneumonia in the 6 persons of Group B was between Nov. 1942 and Dec. 1943.

‡ Persons in Group B were under observation for an average period of 12 months; persons in Groups A, C and D for an average period of 20 months.

of the fact that the questionnaire strained their memories, it is believed that the replies were as reliable as could be obtained from any group. Special care was taken not to disclose the purpose of the investigation until it was completed.

Results. All individuals included in the study were placed in 1 of 4 groups as indicated in Table 1. Tabulation of the number and types of illnesses experienced by the members of each group between Sept. 30, 1942, and May 24, 1944, makes it apparent that those who had primary atypical pneumonia did not acquire any immunity against other varieties of respiratory infection. It should be pointed out, however, that none of the persons who had atypical pneumonia suffered recurrences of this disease, and none of the 75 persons who were free of respiratory infection in August and September 1942 developed atypical pneumonia during the period of study.

The average number of illnesses per person year is essentially the same for all of the groups. The slightly higher figures for Group C are not significant because of the small number of persons (9) included in this group. As expected, the common cold was the most frequently occurring respiratory infection, and the average person, regardless of group, reported approximately 2 respiratory illnesses per year. It is also of interest that 317 (77%) of the total of 413 infections tabulated began during the 10 cold months, November 1942 to March 1943 and November 1943 to March 1944, while only 96 (23%) occurred during the 10 warmer months included in the study.

Summary. 1. The incidence of respiratory illnesses during a period of 20 months following an outbreak of primary atypical pneumonia was found to be the same among 39 persons who had had this disease as among 75 persons who had not experienced this type of infection.

2. It is concluded that primary atypical pneumonia neither confers immunity against nor predisposes to the subsequent development of other common types of respiratory illness.

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INFECTIOUS MONONUCLEOSIS

An Analysis of 26 Clinical and 340 Subclinical Cases

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This presentation is based upon observations made on a series of cases of infectious mononucleosis at Camp McCoy, Wisconsin, from December 1943 to May 1944. The purpose of the discussion is two-

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fold: (1) to analyze the clinical picture, which is similar to that of many other infectious diseases, and (2) to raise the question as to the presence of a subclinical form of this disease, the diagnosis of which depends solely upon laboratory evidence.

"Drusenfieber" was the name given by Pfeiffer[38] in 1889 to the syndrome of enlarged cervical glands, fever, enlargement of the liver and spleen, occurring in children. Filatow,[8] a Moscow pediatrician, had described a similar condition in 1885 but had attached no name to it. Pfeiffer's terminology was translated as "glandular fever" and was so described by Williams[37] in 1897. In the 3rd edition of Osler's "Textbook of Medicine,"[19] published in 1897, this description was repeated. In the following years the disease was frequently confused with leukemia, causing much surprise because all patients recovered. In an excellent review Smeall[26] relates that Professor Hall[10] in 1914 presented such a case before the Royal Society of Medicine, and Osler, who was president of the Society, related another case which had caused him considerable embarrassment by recovering completely. Several others reported similar experiences. In 1920 the disease entered its hematologic period. Sprunt and Evans[28] published a paper on "Mononuclear Leukocytosis in Reaction to Acute Infection." They used the term "infectious mononucleosis" and emphasized the pathologic lymphoid cells characteristic of the disease. Longcope[14] in 1922 suggested that glandular fever and infectious mononucleosis were synonymous. Since then this concept has gradually been accepted among American writers.

Paul and Bunnell[20] in 1932 added an important discovery showing that in cases of infectious mononucleosis the blood serum contained an increased concentration of antibodies against sheep erythrocytes. Later refinements were made by Forssman, Bailey and Raffel,[1] and Barret. It was found that serum sickness would give a low positive titer which could be differentiated by special absorption tests using guinea pig kidney and ox blood. The clinical picture had also become better described by this time. A great variety of findings were reported besides those originally accepted by Pfeiffer. Central nervous system phenomena, skin manifestations and even jaundice were found to occur. Some investigators attempted to classify their cases into "types," designating them by their main presenting complaint. Tidy[34] in 1934 distinguished three main types: glandular, anginose and febrile. At a later date others were added, and Sokal[27] in 1943 described the following five types: glandular, abdominal, respiratory, meningeal and asymptomatic. Therefore, over a period of 50 years the concept of acute infectious mononucleosis has become gradually more varied but more inclusive and better understood.

The etiology of this disease is not definitely known. Murray, Webb and Swann[17] in 1926 isolated *Bacterium monocytogenes*, belonging to the group of Listerella, from spinal fluid of patients. This organism upon injection into rabbits produced a generalized infection associated with an increased number of typical mononuclear cells. In 1929 Nyfeldt[18] reported the isolation of an organism which she called *Bacterium mono-*

cytogenes hominis which also produced a characteristic blood picture upon injection in rabbits. In 1939 the same investigator isolated an organism of the Listerella group by blood culture in 5 cases of the disease.[33] McKinlay[16] found that repeated blood cultures from 50 different cases of infectious mononucleosis were all negative emulsions of fresh glandular substances made during the acute stages and injected into monkeys were without effect. However, Wising, repeating the same experiment, produced mild clinical symptoms consisting of lymphadenitis and an increase in the mononuclear cells in the blood. Van den Berghe and Liessens[35] in 1939 were even more successful and produced a positive heterophil titer in a Macacus monkey injected with emulsions of biopsied glands.

This disease is rarely if ever fatal. Because of this fact the histopathologic picture is confined to biopsy of glands. Gall and Stout[9] did a study on 10 lymph nodes. They state that there is a specific pathologic picture characterized by: (1) marked proliferative activity of the pulp; (2) focal proliferative activity of clasmatocytes; (3) the presence of large numbers of specific infectious mononucleosis cells.

Sprunt and Evans reported definite lymphoid hyperplasia. Pratt[22] reported a reticulo-endothelial type of hyperplasia. Another investigator, Erf,[7] examined scrapings of the inguinal lymph nodes with the supravital staining method. This study showed small transparent spheres or cysts containing a light yellow colored fluid with actively motile brownish black granules. The granules were comma-shaped, L-shaped or irregular shaped and numbered up to 15 to each cyst. The cyst remained intact for a considerable length of time and could be distinguished long after the lymphocytes and the reticulum cells of the lymph nodes had disintegrated. These bodies were alcohol-soluble and for that reason could not be stained in paraffin-embedded blocks.

This disease, though infectious in nature, is believed to be only mildly contagious. Sporadic cases are the usual manifestation. Minor epidemics and small outbreaks have frequently been reported among university students and military personnel. Terflinger[32] in 1908 reported a small epidemic among adults. The next year Burns[4] reported an epidemic in a children's ward. Burnford[3] in 1918 reported an epidemic among soldiers. In 1930 there were 87 cases in the Falkland Islands. A recent outbreak occurred in 1942 in E. M. S. Hospital in Scotland where it became apparent that the infection was widespread in the surrounding district. Steigman[29] reported 20 cases from the American Red Cross Harvard Field Hospital Unit in 1942. Many other epidemics have been reported.

Observations. Over a short period of about 5 months the authors observed a relatively large number of cases of infectious mononucleosis. During the early part of the outbreak there appeared several typical cases which fulfilled the usually accepted criteria for diagnosis. Later the manifestations of the disease became more varied. In an attempt to limit our report to *bona fide* cases and yet to give an inclusive survey of the entire situation, we have classified the cases into four main groups (see Table 1).

TABLE 1.—DATA ON 356 CASES OF INFECTIOUS MONONUCLEOSIS

Group	Total	Typical mononucleosis cells present	Heterophil agglutination titer above the accepted normal 1:56	Clinical picture diagnostic of the disease
I	18	+	+	+
II	8	+	0	+
III	13	+	+	0
IV	327	+	0	0

Group I. Typical cases (18). The patients in this group presented a positive clinical picture, showed the presence in the blood smear of the typical mononucleosis cells and had an elevated heterophil agglutination titer above 1:56.

Group II. Questionable cases (8). The patients in this group presented a diagnostic clinical picture, varied as it might be, also had the typical mononucleosis cells present, but did not at any time during our observation show an elevated heterophil titer.

Group III. Subclinical cases (13). The patients in this group presented no clinical findings and had no history of any acute disease in the preceding 6 months which could have been interpreted as infectious mononucleosis, but typical mononucleosis cells were present and the heterophil agglutination titer was distinctly elevated. These cases were designated as "subclinical cases with positive laboratory evidence."

Group IV. Seronegative subclinical cases (327). The patients in this group presented no clinical findings and gave no history of any illness in the preceding 6 months which could be interpreted as infectious mononucleosis. The heterophil agglutination titer at the time of investigation was negative but all patients showed a large number of cells resembling those of infectious mononucleosis. These cases were designated as "seronegative" and are highly questionable subclinical cases with only partially positive laboratory evidence.

Analysis of Clinical Manifestations in Groups I and II. Frequently the main presenting complaint of an individual case has been used to designate that case as belonging to a certain type. In our observations, most cases seemed to belong to more than one type and it was difficult to determine which was the chief complaint or the most characteristic finding.

In an attempt to classify our series, we listed 16 of the glandular type, 5 of the respiratory type in which cough and nasal discharge were prominent, 3 of the meningeal type in which headache was so marked that a diagnostic spinal tap was done to rule out meningitis, and 2 of the abdominal type where pain in the abdomen was the main complaint. In an analysis of symptoms the order of frequency of some of the clinical manifestations was determined. Table 2 shows this in detail.

1. *Exanthem.* Eight of our cases showed a very definite skin rash. Two of these were practically indistinguishable from the typical rash seen in measles. A third appeared more like the usual manifestation in early scarlet fever. The skin manifestations of this disease have been described by several authors, including Templeton,[31] Tidy,[34] and

Lyght,[15] as a maculopapular eruption, dark red or light pink in color and varying in size from discrete pin-point to large reddish brown purpuric areas. Other authors mention the rash as being vesicular and even urticarial-like lesions have been reported. Sadusk[24] reported confusing the skin lesions of this disease with those of German measles. Templeton also states that 12 of the 17 cases seen by him were practically indistinguishable from German measles.

TABLE 2.—SUMMARY OF CLINICAL MANIFESTATIONS IN THEIR ORDER OF FREQUENCY

	Cases	%
A. Those occurring in more than 50% of the cases:		
1. Malaise	23	88
2. Adenopathy, cervical	18	69
3. Temperature above 102°	18	69
4. WBC above 11,000	18	69
5. Generalized aching	16	61
6. Headache	15	57
7. Spiking temperature curve	14	53
B. Those occurring in less than 50% of the cases:		
1. Adenopathy, generalized	13	50
2. Palpable spleen	9	35
3. Cough	9	35
4. Rash	8	30
5. Chills	7	27
6. Photophobia	7	27
7. Vomiting	5	15
8. Nausea	5	15
9. Abdominal pain	2	7

The incidence of the skin manifestations seems to vary a great deal with individual outbreaks. In one group only 5% of the patients developed a rash, whereas Templeton at the University of California reported that of a total of 91 cases, 18% of them developed a rash. Sometimes antipyretics, barbiturates had been used during the treatment and therefore the question of possible drug eruption confused the picture. We encountered no drug eruptions as far as we could determine.

2. *Fever.* Twelve cases showed a spiking type of septic temperature with peaks reaching as high as 105. daily. The spiking type of curve was the most characteristic finding of the temperature. Total days of temperature over 99.2° varied from 1 day to 14 and appeared to have no bearing on the height of the titer or blood count manifestations. In a few cases the temperature seemed to subside by crisis. Chills were rare.

3. *Adenopathy.* Whereas adenopathy, especially in the cervical region, was one of the early criteria for the disease, we found 7 cases in this series of 26 which showed no adenopathy, either cervical axillary or inguinal, at any time.

4. *Sore Throat and Organisms.* Most of our patients complained of sore throat and showed marked injection and hyperemia of the nasopharynx. A few showed a whitish gray exudate covering the tonsils. Throat cultures were obtained and direct smears were made. All cultures were negative for the hemolytic streptococcus and only 2 cases showed the presence of fusiform bacilli and spirilla. This is in contrast

to a report by York and Eckley[39] who described an epidemic occurring at Cornell University in 1936 consisting of 24 cases, in which there was a high incidence of hemolytic streptococcus in the throats of both well and ill students. More than 50% of the students routinely observed by the health survey at that time showed a positive culture for hemolytic streptococcus.

5. *Malaise.* During the acute episode malaise was usually a minor symptom. The patients felt surprisingly well even at times when their temperature was above 101°.

6. *Palpable Spleen.* In 8 cases the spleen was palpated. This was always one of the later developments during the course of the disease. We never found it before the 10th day; consequently it was no aid in early diagnosis.

7. *Central Nervous System Involvement.* Severe persistent headache occurred in several cases. No true neck rigidity existed and reflexes remained normal. At times the disease suggested meningitis and on several occasions a spinal tap was performed. Only 2 cases had abnormal findings. One of these showed 12 cells, 6 lymphocytes and 6 neutrophils, and a positive Pandy test. The other showed 12 cells, all lymphocytes, and a negative Pandy. There were no residual findings and the symptomatology consisted of headache and moderate drowsiness.

Several cases of acute infectious mononucleosis with central nervous system involvement have been reported. In 1931 Epstein and Dameshek[6] reported 1 case showing 35 monocytes present in the spinal fluid and having a palpable spleen, generalized adenopathy and a typical blood picture. The significance of the heterophil agglutination test had not yet been discovered at that date. Johansen[12] reported another case which showed 16 monocytes in the spinal fluid with marked neck rigidity, awkward speech, impaired memory, and headache of 2 weeks duration. In 1938 Pietzonka[21] presented 3 cases having nuchal rigidity, severe headache, injected tonsils, sore throat, an enlarged spleen, a heterophil agglutination titer up to 1:64, and 29 monocytes present in the spinal fluid. Schmidt and Nyfeldt[25] in 1938 reported 5 cases which showed up to 26 monocytes and as high as 115 lymphocytes present in the spinal fluid but with few meningeal or cerebral symptoms. Thelander and Shaw[33] in 1941 reported 6 cases of infectious mononucleosis with marked symptoms of cerebrospinal involvement. One case showed a spinal fluid cell count of 630 with 70% lymphocytes.

Landes, Reich and Perlow[13] in 1941 reported a new aspect of the disease. The cerebral involvement was very extensive and the clinical picture was that of an acute ataxia with marked involvement of the cerebellar system. The protein in the spinal fluid was increased to 170 mg. per 100 cc. but the cell count remained below 9 lymphocytes. The heterophil agglutination titer was 1:1024. The overall picture in this case was that of an encephalitis. Zohman and Silverman[40] in 1940 described a case associated with evidence of diffuse lower motor

neuron disease. The patient had complete flaccid paralysis of all four extremities. There were noted fibrillary twitchings of his right arm, no sensory disturbances, no atrophy; however, all deep reflexes were abolished.

8. *Abdominal Pain.* The outstanding symptom occurring in a 27 year old woman was generalized abdominal pain which persisted for 2 days. There was no localized tenderness or muscle spasm. The temperature ranged up to 102°. Nausea and vomiting were her only other complaints. On the 5th day the heterophil titer was elevated up to 1:896. Her convalescence was rapid and she was discharged on the 15th day. Sokal refers to this syndrome as the "abdominal type."

9. *Cough.* Seven of our cases complained of a persistent, racking, non-productive cough, somewhat similar to the cough noted in measles. Chest examination was essentially negative except for occasional moist râles in bases. This symptom usually disappeared within 6 days.

10. *Vomiting.* Vomiting was noted in only 2 cases. It was not in any way significant except that it occurred in the one case where abdominal pain was the main symptom and in the other with severe headache tending to confuse the diagnosis.

11. *Leukocyte Count.* Early in the disease, a marked leukocytosis may occur as high as 35,000 with an increase in the neutrophils in most cases. This is usually followed by leukopenia and an associated rise in the total lymphocyte count. The typical mononucleosis cells were often not present until the total lymphocyte count had increased. We are unable to confirm the statement that the degree of leukopenia was related to the height of the titer.

12. *Kahn Test.* In this entire group there was not a single positive reaction to the Kahn test. This differs from many other reports.

13. *Epidemiology.* Among the 26 cases described in Groups I and II, there were only 3 cases with proved contact, 2 nurses and a laboratory worker. The great majority of Groups III and IV, consisting of 340 cases, came from one unit where contact in barracks may be presumed to have been close.

14. "*Type.*" Even though it is difficult to classify the patient who has 4 or 5 complaints into any one type, a superficial grouping was made. We included respiratory, glandular, abdominal and meningeal types. We believe the listing is of some value inasmuch as it stresses the diversity of the clinical symptoms of this disease and helps to suggest the diagnosis in cases in which it would otherwise never be considered.

Discussion of Groups III and IV. Early during the outbreak of this disease it was observed that a large number of patients in the hospital with no complaints relative to this disease, had typical mononucleosis cells. For a time these were disregarded as insignificant. However, later the consistency of the findings became disturbing and it was decided that some attempt at evaluation and explanation of the presence of these cells should be made.

It had been observed that several of our clinical cases came from

one particular unit. This unit consisted of 600 men engaged in combat training and in apparent excellent health. Blood smears were obtained from 522 men and 217 (41%) revealed the presence of occasional abnormal cells resembling typical mononucleosis cells. About 47% of 101 cases of this group showed over 5% of these cells present in the differential count. An attempt was made to do heterophil titer determinations on this entire group. Only 74 were obtained and these showed the following results:

TABLE 3.—INCIDENCE OF CASES ACCORDING TO TITER

Titer	No. cases
Negative	14
1:7	9
1:14	19
1:28	19
1:56	5
1:112	5
1:224	3

The final results showed the presence of 13 cases with typical cells and a titer above 1:56. These represent the Group III cases. None of them gave a history of illness during the preceding 6 months which could be interpreted as being infectious mononucleosis.

Group IV consists of 314 cases which had only the typical cells without elevated heterophil agglutinations and without clinical findings or a past history of illness suggestive of this disease. It is composed of 110 hospital patients admitted for other complaints and 204 cases from the unit survey. A percentage cell count showed that 226 had less than 5% typical cells present and that 88 varied from 5 to 20%. This group consists of the highly questionable cases in which the diagnosis rests entirely on the blood findings. Similar groups have been reported. The most carefully described is that of Reyersbach and Lenert[23] who, in 1941, studied 16 cases which had no symptoms and no physical findings of any kind and in which the Paul-Bunnell test was uniformly negative. The epidemic occurred in a convalescent home for children with rheumatic fever where leukocyte counts were done at regular intervals as a part of the medical routine, also temperatures and pulse rates were taken 3 times daily. In general, the patients were under close medical observation so that no marked symptomatology could have escaped notice. We were not able to do as thorough a check-up in our cases. A few of this group may have had minor symptoms which were not reported to their dispensaries and for which they were not hospitalized.

As the only criterion of this large group was the presence of the characteristic infectious mononucleosis cell, our attention was focussed on its morphology. The various descriptions present in the literature were carefully reviewed and it was decided that from its appearance the cell could be divided into stages of development. The young cell resembles a normal small lymphocyte except that the small rim of cytoplasm stains a deep and characteristic blue color. The next stage

is a larger cell with an oval or kidney-shaped nucleus and a moderate amount of cytoplasm that stains a homogenous deep blue color. The third stage presents the most easily recognized appearance. The cell is large and the cytoplasm is generous and fragile and tends to spread irregularly on the differential smear. The deep blue cytoplasm is most intense in the periphery and fades toward the nucleus. Wherever the cytoplasm is traumatized in making the smear there tends to be produced a triangular wedge of denser accumulation of deep blue stain. The nucleus is large and may be round, kidney-shaped, or irregularly lobulated and the chromatin is distributed in a lace-like pattern that is unlike lymphocytes or monocytes.

Several authors have suggested that these abnormal cells without the confirmation of an elevated heterophil titer should be regarded as an "irritation" form of lymphocytes which are liberated into the blood stream as a response to a variety of foreign proteins. Warren[36] states that a study of blood smears from a variety of cases, including upper respiratory infections, sinusitis and others showed characteristic mononucleosis cells from 1 to 10% in a differential count. Similar observations have been made by Baldridge,[2] Downey,[5] Stuart and Cunningham.[30] However, 204 cases in our group were in excellent health and the other 110 had no illness in which a foreign protein reaction could be suspected. It is also significant that this group of cases was found at the same time that the clinical cases were most frequent. The correct evaluation of the hematologic findings is as yet not completed.

Treatment. The treatment of this disease has been mainly symptomatic. Analgesics and antipyretics are useful as measures to make the patient more comfortable. Hot irrigations in cases of sore throat have been found beneficial. Sulfonamide therapy has been recommended, however, when this was used in our series it proved ineffective. Penicillin was used in 3 cases without beneficial results. Convalescent serum has been highly recommended by some authors but it was not used in this series. Three cases with marked throat ulcerations were treated with repeated small doses of mapharsen. Two of these responded very dramatically, but the third showed negligible results. Bismuth salts intramuscularly have been advocated[11] but were not used in this series. The disease appears to be self-limited, usually presenting no longer than 10 days of acute illness, and for that reason too vigorous therapy seems inadvisable.

Conclusions. 1. The outstanding feature of this disease is its protean manifestations which may mimic many other diseases, such as measles, German measles, scarlet fever, meningitis and pneumonia.

2. Early in the disease the laboratory findings are inconclusive and the diagnosis must be made by exclusion. A spiking fever, an exanthem, a non-productive cough, headache, and marked leukocytosis proved to be the most common early findings.

3. Marked leukocytosis up to 35,000 with a high percentage of neutrophils occurred in many cases early in the course of the disease. This was usually followed by a leukopenia with an increase in the

absolute lymphocyte count. The typical mononucleosis cells were present in greatest number when the leukopenia was well established.

4. There appears to be no correlation between the clinical severity of the disease and the height of the titer or the percentage of the mononucleosis cells present.

5. We have no explanation for the large number of subclinical cases which were "seronegative" and which showed only the presence of mononucleosis cells in the blood smear. There is no question that these cells were as typical as any described in the literature. Whether or not their presence is pathognomonic or whether there is such a thing as "irritation phenomena" remains to be answered.

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A COMPARISON IN MAN OF SULFATHIAZOLE AND 2-SULFANILYL-3-5 DIHYDROTHIAZOLE (SULFATHIAZOLINE, SULFAHYDROTHIAZOLE)*

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Sulfathiazoline† (2-sulfanilyl-3-5 dihydrothiazole, sulfahydrothiazole), synthesized by Raiziss and Clemence,[5] differs from sulfathiazole by 2 additional hydrogens in the thiazole portion of the molecule. It has been shown by Raiziss, Severac, and Moetsch[6] that the therapeutic effect of sulfathiazoline equaled that of sulfathiazole in experimental pneumococcal and staphylococcal infections in mice and that the drug was readily absorbed from the gastro-intestinal tract of the same species. Further studies by this same group, as well as by Kolmer, Rule, and Groskin,[4] suggested that sulfathiazoline was no more toxic in experimental animals than sulfathiazole.

The present report describes observations dealing with the absorption, excretion, and toxicity of sulfathiazoline in man.

Fate of a Single Dose. Ten adult patients, convalescing from various medical conditions and showing no evidence of gastro-intestinal, hepatic, or renal disease, were each given a 3 gm. dose of sulfathiazoline by mouth, shortly after a light breakfast. Drug concentrations in blood and urine were determined by the method of Bratton and Marshall.[1] Within 2 hours the average concentration of free drug in blood was 2.4 mg. per 100 cc. (Table 1), while the highest level reached

Table 1.—Fate of Single Oral Dose (3 Gm.) of Sulfahydrothiazole (Averages of 10 Patients)

	Blood			Urine			
Time (hrs.)	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetylated (%)	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetylated (%)	Dose excreted (cumulative) (%)
2	2.4	3.1	22.6				
4	3.8	5.8	26.3	27.5	36.6	24.8	3.4
6	2.6	3.7	29.8				
8	2.3	3.5	34.3	106.5	153.5	30.6	20.4
24	1.1	1.8	38.8	82.4	129.4	36.3	49.8

* This work was aided by a grant from The Abbott Laboratories, Philadelphia, Pa.

† This drug was supplied through the courtesy of Dr. G. W. Raiziss, Director of the Dermatological Research Laboratories, Division of Abbott Laboratories, Philadelphia, Pa.

in any 1 patient at this time was 4 mg. per 100 cc. The concentration of free drug showed little further change and at the end of 4 hours the average concentration was 2.8 mg. per 100 cc., the highest average level observed. Average levels above 2 mg. per 100 cc. were maintained for 8 hours. In similar experiments with sulfathiazole, higher average concentrations prevailed during the first 8 hours following administration of the drug, while at 24 hours comparable levels were observed. An average of 30% of the drug was present in the acetylated form in these patients throughout the 24 hour period.

Excretion of sulfathiazoline in urine (Table 1) was less than that of sulfathiazole[7] under comparable conditions, averaging half of the administered drug within 24 hours, whereas 60 to 90% of sulfathiazole was excreted during this time. During the first 24 hours an average of 31% of drug found in the urine was present as acetylsulfathiazoline.

Effect of Continued Administration. Thirty-three adults, suffering from pneumococcic pneumonia, were treated with sulfathiazoline. All patients were given an initial 3 gm. dose by mouth which was repeated in 4 hours, then followed by 1 gm. every 4 hours until the temperature remained normal for 48 hours along with evidence of clinical improvement. The average total dosage of drug was 29 gm. Concentrations of free and total sulfathiazoline in blood were determined in samples collected each morning during the time of drug therapy. The average concentration of free drug was 3.3 mg. per 100 cc., with concentrations ranging from 2 to 5.7 mg. per 100 cc. Again, this is only about three-fifths of the average level attained during sulfathiazole therapy. The concentration of acetylsulfathiazoline averaged 1.5 mg. per 100 cc., or 31% of the total drug present in the blood.

Toxicity. Of the 33 patients treated with sulfathiazoline, 8 developed untoward reactions attributed to the drug. Vomiting occurred in 6 patients, being mild in 3, moderate in 2, and in one instance necessitating the discontinuance of the drug. Individual cases of skin rash, hematuria, and neutropenia were observed. Crystals containing sulfathiazoline were observed frequently in the urine of patients. The toxic manifestations of sulfathiazoline appear to be about the same as sulfathiazole in the treatment of pneumonia.[2]

Therapeutic Action in Pneumonia. Although the response of the group treated with sulfathiazoline was better than that of much larger groups when sulfathiazole or sulfadiazine were employed, the patients comprising the sulfathiazoline treated group presented mainly moderate or mild illness, while those employed for the evaluation of sulfathiazole[2] and sulfadiazine[3] included pneumonias of all degrees of severity so that direct comparison is misleading. Of far greater significance is the observation that 5 patients showing little or no response to sulfathiazoline, improved promptly following substitution of sulfathiazole or sulfadiazine.

It is our opinion that sulfathiazoline is less efficacious for treatment of pneumonia than sulfonamides currently in use.[3] Our observations were limited to this disease and do not necessarily provide any indication of its effectiveness in other conditions.

Summary. 1. Concentrations in blood and excretion in urine are less following oral administration of sulfathiazoline in man than with sulfathiazole in equivalent amounts.

2. The toxic effects observed following sulfathiazoline are comparable with those encountered following sulfathiazole in the treatment of pneumonia patients.

3. Sulfathiazoline appears to be less satisfactory for treatment of pneumococcic pneumonia than sulfathiazole or sulfadiazine.

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TREATMENT OF HYPERTHYROIDISM WITH A COMBINATION OF IODINE, THIOUREA IN SMALL DOSES, AND DESICCATED THYROID

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Thiouracil rather than thiourea has commonly been employed in this country for the treatment of hyperthyroidism, largely because thiourea is less effective than thiouracil, gram for gram, in the production of goiters in young rats. A few clinical observations also suggested that it might be less effective in the treatment of hyperthyroidism.[1] Furthermore, thiourea medication occasionally produced a dermatitis and was often associated with an unpleasant odor of the breath.[1,5,10,12,13,14,15,16] Unfortunately thiouracil has proven a somewhat dangerous drug, since its use over prolonged periods produces toxic reactions, especially granulocytopenia, in about 11% of all patients treated with it.[3,4,6,7,12] This fact has led us to reinvestigate the clinical effectiveness and toxicity of thiourea in smaller doses than

those previously employed. Contrary to the prevalent impression, thiourea in these doses has been found to be a highly effective agent in the treatment of most cases of hyperthyroidism. A plan of therapy has been evolved using both iodine and thiourea. Some patients also receive desiccated thyroid.

Materials and Methods. Twelve patients with hyperthyroidism,* some hospitalized and some ambulatory, were first treated with 5 to 15 drops daily of strong solution of iodine, U.S.P. (Table 1). After the remission with iodine therapy had reached its maximum, thiourea was started in doses varying between 0.05 and 0.28 gm. once daily. Two patients for a time received larger amounts, up to 0.80 gm. daily, in divided doses. Those patients whose level of serum precipitable iodine fell below normal received 0.06 gm. of desiccated thyroid daily as well. In some instances iodine medication was later discontinued. Four other patients with hyperthyroidism received thiourea without a preliminary course of iodine administration (Table 2). The diagnosis of hyperthyroidism was based on the usual characteristic clinical features of the disease together with an increased concentration of precipitable iodine in the serum and, usually, an increased basal metabolic rate.[8] Various clinical types of hyperthyroidism were included.

Serum precipitable iodine, basal metabolic rate, body weight, pulse rate, erythrocyte and leukocyte counts, size of the thyroid gland, and general clinical condition were carefully followed throughout the entire course. In a few patients the concentration of thiourea in the ultrafiltrate of serum 12 hours after the ingestion of the daily dose was measured.[2]

Results. The results in patients treated with iodine, thiourea, and desiccated thyroid are presented in Table 1, those in patients treated with thiourea alone in Table 2.

(*a*) *Iodine Administration Alone.* Preliminary iodine medication diminished the severity of the hyperthyroidism for a time in most of the patients in Table 1, but failed to produce a complete and lasting remission. In 2 instances (JH and JO) the disease had become progressively more severe after the initial remission under long-continued iodine therapy. Certain exceptional patients in whom iodine did produce a complete and lasting remission were excluded from the group selected for thiourea therapy.

(*b*) *Iodine and Thiourea Therapy.* Administration of thiourea as well as iodine resulted in a complete disappearance of the signs of thyroid overactivity and depression of serum precipitable iodine to normal or subnormal in 11 out of 12 instances. Even in the 1 partially refractory case (JO) 800 mg. of thiourea daily produced a distinct drop in the serum precipitable iodine with concomitant clinical improvement. Three cases responded well to only 100 mg. of thiourea daily.

(*c*) *Iodine, Thiourea, and Thyroid Therapy.* Thiourea medication depressed the serum precipitable iodine below 3 gamma % in 4 patients (Table 1). Levels as low as this are characteristic of myxedema,[17] and are never found in euthyroid subjects. The basal metabolism tended to fall more slowly than the serum precipitable iodine, and so was usually normal when the iodine first fell below the normal range. These 4 patients were then given daily maintenance doses of 0.06 gm. of desiccated thyroid. The concentration of precipitable iodine in

* We are indebted to Dr. M. Heinemann for the opportunity to follow 3 of these patients.

TABLE 1.—TREATMENT OF HYPERTHYROIDISM WITH IODINE, THIOUREA AND THYROID

Patient	Age	Sex	Daily dose*			Time from start (wks.)	Body weight (kg.)	Pulse rate (per min.)	BMR (%)	Serum precipitable iodine (gamma %)
			Strong solution iodine (drops)	Thiourea (gm.)	Thyroid (gm.)					
BP	26	F				0	49.6	82	+41	15.2
			10			4	50.8	78	+16	9.5
			10			10	50.9	76	+26	12.9
			10	0.10		15	52.0	96		6.0
			10	0.10		19	52.8	76	+ 3	3.7
			10	0.10		23	54.9	64	−14	3.2
			10	0.10	0.06	28	52.1	74	+ 8	5.8
			10	0.10	0.06	36	50.0	80	+ 1	7.0
MS	70	F				0	46.1	94	+43	8.9
			15			2	46.5	80	+19	6.0
			15	0.28		7	46.2	80	+ 4	5.1
				0.28		12	48.1	84	+10	3.3
				0.28		22	48.6	86	+17	0.6
				0.28	0.06	28	49.2	76	+19	6.5
EB	37	F				0			+14	
			15			8	55.7	96	+ 9	18.9
			5			9	56.2	104	+11	10.9
			5	0.28		14	59.4	82	+12	4.1
			5	0.28		18	59.3	78	− 8	3.8
			5	0.28		22	60.2	72	− 9	4.8
			5	0.28	0.06	32	60.5	86	+ 5	5.1
EG	60	F				0	53.0	84	+37	10.6
			5			2	52.4	70	+ 8	7.0
				0.28		5	54.5	84	+23	
				0.28		9		72		4.1
				0.28		18	55.0	72		1.3
				0.28	0.06	31	55.2	60		4.0
JH	57	M				0			+67	
			5			16	52.2	84†	+55	11.4
			15	0.70		18	52.2	52	+42	5.1
			15	0.70		22	57.5	56	− 3	0.9
			15	0.56		24	60.4	60	+ 6	4.5
			15	0.28		28		60	−10	1.6
			Thyroxine studies‡							
				0.28	0.06	31	60.1	86	+20	5.9
			15	0.28	0.06	60	61.0	60	+ 6	4.3
MK	54	M				0	64.0	88	+44	9.0
			15	0.28		1	63.8	76	+33	7.9
				0.28		5	67.2	72	+19	7.6
				0.28		14	67.7	60	+11	5.8
				0.28	0.06	25	68.2	64	+ 9	5.7
				0.28	0.06	31	67.6	64	+19	5.0
AP	26	F				0	53.4	80	+36	10.5
			15			2	52.8	68	+ 1	6.6
			15			6	56.9	84	+17	7.3
			5	0.05		10	56.2	80	+10	8.8
			5	0.10		14	57.4	70	+10	4.5
			3	0.20		21	57.8	60	− 6	2.2
SL	57	F				0			+35	
			5			22	49.9	84	+41	9.8
			5	0.28		25	50.4	86		9.6
			5	0.28		29	49.9	66	− 1	6.8
			5	0.28		39	53.5	82	+ 1	3.0
SB	45	M				0	57.0	50	+28	10.9
			15	0.28		8	58.8	66	− 1	3.4
			2	0.20		38	63.3	70	+13	6.2
JO	39	F				0				
			15			75	55.8	100	+85	48.2
			15			78	52.0	94	+80	27.5
			15	0.40		81	50.8	84	+85	17.2
			15	0.80		82	50.0	84	+84	14.8
						Thyroidectomy				
PG	37	M				0	60.8	72	+42	22.2
			15			3	62.8	72	+12	7.7
			15	0.28		7	64.4	68	+13	7.1
			15	0.28		14	64.2	60	−16	4.5
EC	53	M				0	74.0	66	+22	10.2
			15			5	72.4	60	+20	14.1
			15	0.10		11	72.0	100		14.3
			15	0.28		17	69.2	60	+15	12.5
			15	0.28		24	67.4	70	+19	6.3

* During interval ending with the time indicated in the same row. † Auricular fibrillation. ‡ Not reported here.

serum promptly returned to and was maintained at normal levels. In 3 cases (BP, EB, MK) thyroid medication was begun before the serum precipitable iodine had declined below normal.

TABLE 2.—TREATMENT OF HYPERTHYROIDISM WITH THIOUREA ALONE

Patient	Age	Sex	Daily dose* thiourea (gm.)	Time from start (wks.)	Body weight (kg.)	Pulse rate (per min.)	BMR (%)	Serum precipitable iodine (gamma %)
WB	46	M		0	70.8	74	+44	9.5
			0.10	4	69.6	76	+43	8.5
			0.10	7	66.2	52	+19	5.7
KM	58	F		0	74.7	88	+32	10.3
			0.28	3	73.2	58	+15	6.4†
JC	15	M		−2	47.5	128	+16	22.5
				0	45.0	100	+ 7	15.4
			0.28	1				6.5
			0.28	4	51.4	78	−12	7.4
			0.28	9				7.7
MW‡	49	F		−1	60.2	80	+37	19.1
				0	59.2	84	+31	12.0
			0.28	1	58.5	80	+35	12.7
			0.28	3	56.6	80	+17	8.9
			0.28	8	61.4	90	+29	9.1

* During interval ending with the time indicated in the same row.
† Patient stopped thiourea 6 months later: hyperthyroidism promptly recurred.
‡ Serum iodin 5.5 and BMR −17 after 12 weeks of treatment.

(*d*) *Thiourea Therapy Alone.* The data from the 4 cases in Table 2 indicate that thiourea alone without preliminary iodine medication may also induce a remission in hyperthyroidism, although it was incomplete in 1 case (MW) after 8 weeks. From Table 1 it is clear that thiourea alone may under some circumstances maintain a remission originally induced by a combination of iodine and thiourea medication (MK), and may even result in a subnormal level of serum precipitable iodine (MS, BG).

(*e*) *Rate of Response to Thiourea.* In view of the variability of response from case to case it cannot be determined from the limited data in Tables 1 and 2 whether preliminary medication with iodine retards or accelerates the response to thiourea. In 2 cases the response appeared within 1 to 2 weeks; 1 (Table 1, JH) had been receiving iodine for a long time, the other (Table 2, JC) had received none. Other cases in both groups only responded after a considerably longer interval.

(*f*) *Toxic Reactions.* No change in erythrocyte, leukocyte, or differential count of the blood and no urinary abnormalities developed in any patients. A mild halitosis was common. There were no skin eruptions and no febrile reactions. In 1 subject (KM) 0.28 gm. of thiourea daily occasionally produced nausea and vomiting after 6 months of therapy. In another (JO) there was some nausea while taking 400 to 800 mg. daily, but no vomiting. No distinct change in the size or consistency of the goiter and no change in exophthalmos could be detected in any patient.

Discussion. Evidently thiourea in daily doses of 0.100 to 0.280 gm. can produce a satisfactory sustained remission in cases of hyperthyroidism which have previously been brought into partial remission by iodine medication alone. This fact effectually disposes of any theory that previous treatment of the hyperthyroidism with iodine seriously interferes with the action of thiourea. Cases with toxic adenoma and those with diffuse goiter both respond. On the other hand, it cannot be asserted on the basis of the evidence available that there is any true synergistic action between the two types of treatment, since thiourea alone in the same dosage is at times capable of inducing and maintaining a remission. Further observations bearing on this question are now in progress.

The frequency with which the serum precipitable iodine is depressed below normal during continued thiourea medication proves that hypothyroidism is easily produced. Restoration of the serum precipitable iodine to a normal level with a dose of 0.06 gm. of thyroid daily suggests that the larger doses sometimes advocated[11] may be excessive. The lag in the fall of the basal metabolism behind that of the serum precipitable iodine indicates that thyroid medication should be instituted *before* the basal metabolism has fallen and clinical myxedema has appeared. It might well be sound practice routinely to begin thyroid medication as soon as remission of the hyperthyroidism is well established, and to discontinue it only if signs of toxicity recur. This should be especially important if, as seems likely, progression of exophthalmos and of the goiter is favored by functional hypothyroidism.[9]

No conclusive advantages can at present be claimed for the régime which is described here over the commoner form of treatment with thiouracil alone. On the other hand, it is apparently at least as effective in most instances and has the *a priori* advantage that toxic reactions should be minimized by reliance on small doses. It also provides a preliminary reduction of glandular hyperplasia by iodine medication, which should be a distinct advantage should operative intervention become desirable. It is as yet too early to estimate the permanency of the remission obtained with this régime.

These observations clearly illustrate the high sensitivity of the hyperthyroid human subject to thiourea in comparison with that of the normal experimental animal. The effectiveness of these small doses of thiourea suggests the existence of a peculiar sensitivity or avidity of the hyperthyroid patient for thiourea, particularly in view of its effectiveness in spite of the low concentrations of thiourea in serum 12 hours after the single daily dose (0.4 mg. % or less). Assays of relative goitrogenic potency of different therapeutic agents in the normal animal yield results which cannot be applied directly to the human subject. It may reasonably be considered whether the search for goitrogenic substances of higher and higher specific potency is of comparable importance to the search for compounds producing few idiosyncratic reactions. Whether thiourea in small doses is such a substance can only be established by extensive clinical trial.

Conclusions. 1. Small doses of thiourea, 0.10 to 0.28 gm., given once daily, usually produce and maintain a satisfactory remission in patients with hyperthyroidism previously treated with iodine.

2. The serum precipitable iodine is commonly depressed to myxedematous levels if these doses of thiourea are continued for some weeks, even before the basal metabolic rate has fallen to subnormal levels. Desiccated thyroid, 0.06 gm. daily, suffices to restore euthyroid concentrations of serum precipitable iodine.

3. Iodine medication does not inhibit the action of thiourea. Whether it delays or whether it accelerates or synergizes the response to thiourea is as yet uncertain.

4. A therapeutic régime for the medical treatment of hyperthyroidism based on these observations is described.

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PROTEST. A RECORDED PSYCHIATRIC PROGRAM*†

By Major Albert A. Rosner, M.C., A.U.S.
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Commentator: This composite recording[1] is made to illustrate some extreme forms of protest adapted and voiced by soldiers in the military service.

* The neuropsychiatric department of this hospital is preparing a voice-recorded psychiatric library reflecting psychiatric problems encountered in the military service. Recordings are made, with the patient's full knowledge, on a Constant Groove-Speed Reference Recording Machine, using thin, pliable, transparent composition disks, each capable of running for a 1-hour period. (Frank Reiber, Inc., Los Angeles, Calif., U. S. A.)

This is one of a series of recordings on the general subject of failure in the military service. Recorded sequences of original interviews are transcribed, with added commentary, to a single composite disk. Playing time of this disk: 27 minutes.

The recorded library will be available for reference at the Army Medical Library, Washington, D. C.

† Presented phonographically before the Section of Neurology and Psychiatry of the New York Academy of Medicine and The New York Neurological Society, March 13, 1945, at the New York Academy of Medicine, New York City.

As a form of contradiction, protest is a natural and understandable phenomenon. Protest may be conscious, deliberate, and self-assumed, representing legitimate complaint against a disagreeable environmental situation. This is its most apparent and commonplace form. The restrictions of military life and the disciplines imposed by it are very generally unwelcome and are accepted only by compromise. Some, possibly more capable than others of meeting this threat to self-assertion and ego-esteem, absorb this mode of life without demur. Others, more refractory, accept it under protest. Protest, for them, affords natural and self-determined release and serves as an automatic auto-therapeutic mechanism, often an adequate form of cathexis.

Protest may be legitimate or illegitimate, justifiable or reprehensible. Protest may be verbal or non-verbal. It may be wholly behavioristic, and registered as departure from usual or normal behavior. It may be conscious or unconscious. It may be sane or insane. Irrespective of its form, it is usually articulate and recognizable.

Protest is an aggressive rendition that contradicts authority. It is a "combat reaction" due to real conflict between the individual and his environment. Conflict of this type begets symptoms. In these recordings, these symptoms, in a literal sense, are permitted to speak for themselves. Their importance, from the point of view of the military, becomes more and more obvious as one gives ear to the soldier sweating and straining under his burden.

CASE 1. *Protest as dementia præcox.* Interview:

"What was it that brought you to the hospital ten days ago?"

"I had a run-in with an officer. I had on my fatigues and my slippers and was walking down the avenue without a hat, with my hands in my pocket. Naturally the lieutenant stopped me. He called me 'soldier' and I guess I did not like it. I flew off of the handle. He told me to halt, but I did not halt. He held out one arm and tried to stop me. I blew off and went to hit him, but another officer stopped me. Then he and the M. P. had me arrested and I was taken to the Public Relations Building."

"While you were in that building something else happened from what I could gather. Can you tell me what that was?"

"I was walking around in that building and was pretty keyed up, and I saw a picture of the colonel in a desk basket."

"Colonel, who—which colonel?"

"The commanding officer of the Post."

"What did you do?"

"I seized the picture, tore it up, and threw it on the floor."

Later:

"Now what was it, George, that you told me the other day about those fellows in the barracks talking in such an odd and unusual way?"

"Well, they apparently knew something about my past, and practically everything they said reflected on my past. They all seemed to have me involved."

"You seemed to be the center of all of this conversation?"

"Yes, sir, I seemed to be in the middle of it all."

"What is this about a girl that you mentioned before?"

"I think I have seen her here on the field. It seems to have been related to my being arrested and put in the stockade. I have seen her on the field in various automobiles. I thought possibly she was going out with the Commanding Officer of the Post. I thought that the FBI originally was involved in the affair, but now I don't know."

"Now, when you look back upon the whole incident, how does it appear to you?"

"It appears that I had a poor perspective. Things seemed to be out of focus."

CASE 2. *Protest as hysteria.* Interview:

"Now, what is your trouble, James, how long have you been in the hospital?"

(*Breathlessly*) "I don't know how long I have been here. They gave me shots and my whole body got paralyzed and I have been paralyzed ever since."

"Tell me more about it."

"I am weak."

"Why do you breathe so heavily, are you out of breath?"

"I am just weak."

"You seem to be fairly upset about something."

"I am all right."

"Why can't you walk?"

"My legs won't hold me. I fall."

"Do you sleep all right at night?"

"No sir, I don't know why. (*Desperately*) I just can't breathe!"

"How long have you been in the army, James?"

"About two years. I have never been in the hospital before. They gave me shots the other day and I became stiff all over, and I have been like this ever since. First they gave me five shots, and the other day they gave me four, and then something happened."

CASE 3. *Protest as suicide.* (Mental age: 9 years, 2 months.) Interview:

"Ralph, I want you to tell me what it was that brought you to the hospital about a week ago."

"Well, sir, they said I drank iodine."

"Did you take iodine?"

"I don't know, sir—I don't know. I don't understand it."

"Have you been having a pretty tough time of it in the army?"

"Well, sir, I have."

"What has been the trouble?"

"I have been getting headaches."

"Headaches. And you have been worried about something, haven't you?"

"Well, sir, I was worried about the farm. They need me there, sir."

"And you have been concerned about the chickens too?"

"Yes, sir, I was."

"The other day you became all upset about one of the ward-boys and chickens. Do your remember? You were listening to some music, I think, at the time."

"About the records, sir?"

"Yes, tell me about that."

"Oh, them records, I cannot understand them, sir. I don't know—they just boom, boom all day long, sir."

"Are they jazz records?"

"I don't know what kind of records they are. I never heard records like them before."

"Are they symphony records?"

"Yes, I think that is what you call them. They go *boom, boom* all day long."

"Have you ever heard records like that before?"

"No, sir, I don't like them."

"What about the rooster?"

"Oh, the rooster. I cannot understand the rooster crowing at night here. I never heard that before."

"Why did you get so upset the other day?"

"Well, they would not let me go over to see the chickens."

CASE 4. *Protest as reaction to overseas assignment.* Commentator:

This 20 year old sergeant was brought to the attention of the psychiatric department a week ago, having been brought to the hospital in an ambulance from a downtown cafe. It is stated that while drinking there, he suddenly

felt dizzy and fell to the ground. He was picked up and brought directly to the hospital. This patient, at first, was considered an epileptic. The next day the patient was fully alert and requested to be returned immediately to his group. An investigation of this soldier's army background revealed that he had advanced by series of promotions to a position as Staff Sergeant, and that he was considered a reliable and conscientious non-commissioned officer.

A few hours after leaving the hospital, the patient reported to the Outpatient Department of the Psychiatric Section and stated that he was unable to remain on duty. He appeared to be in an acutely agitated condition. He was admitted directly to the hospital. He stated, on this occasion, that he had failed to give the psychiatrist the whole story during his previous hospital stay.

Interview:

"Now, Gene, I want you to tell me about the situation which brought you to the hospital. I am referring to the first time you came here."

"I was brought here in an ambulance. I don't remember all the details. I fell on the street and I cannot remember all the details. I told one boy that I did not feel very well, then I fell down."

"How were you when you first came to the hospital in the ambulance, or do you remember?"

"All I remember I was all tight inside. My stomach and head was going around. I don't remember everything that happened very well. I remember waking up on the ward."

Later:

"Now, would you say that this nervousness was brought on in any way by the prospect of going overseas?"

"I don't see why it could be because when I came down here I knew I was going overseas. I volunteered to go over."

"You get along well with all the fellows in your outfit, don't you? They think you are a regular fellow, don't they?"

"Yes, sir, that's true. They have a high regard for me."

"And you earned your promotions because of ability, is that not so?"

"Yes, sir, that's true. I did my job pretty well."

"Is this sort of reaction more or less of a surprise to you?"

"Yes, sir, it is."

Later:

"I don't want any discharge, sir. I have been doing my job for two and one-half years."

"When you say you don't want a discharge, what do you mean?"

"Everybody seems to think I am bucking for something."

"Well, who says that you are?"

"Well, I cannot say definitely, but it is what I think. I just want you to know, sir, that I am not a 'goldbricker'."

"Are you afraid?"

"Yes, sir, I am now."

"Of what?"

"Of going overseas."

Commentator: Intravenous sodium amytal is administered to this patient. The tourniquet is applied and needle is inserted in the antecubital vein. Patient is quite agitated throughout the procedure, but coöperates as fully as he is able.

Interview:

"What's the trouble, Gene, why are you so upset?" (*The patient is too agitated to answer. He cries constantly.*)

"Tell me, Gene, why are you so upset?"

"I just want my wife. I want my wife. Where is she? I want her here."

"Would you care to see her in your present state?"

"I want her here. I want her here." (*Voice rises to a wail.*)

Later:

"Have you been crying a great deal in the last few days?"

"No, not very much."
"Did you ever cry like this before in your life?"
"No, sir, I never have."
"Is this a new experience for you, Gene?"
"Yes, sir, it is."
"What makes you worry about your family so?"
"I just don't want to go overseas."
"Why is that, can you tell me?"
"I don't want to go over that's all. I am scared and I am nervous." (*Continues to cry.*)
"Gene, if we can get you over this feeling, do you think you can make a go of it?"
(*With fine show of spirit.*) "I want to do my part!"
CASE 5. *Protest as hysterical dysphonia.* Interview:
"How long has it been, Arnold, since your voice has been this way?"
(*In a harsh whisper.*) "I started last June."
"You mean that you had an attack like this wherein you could not talk above a whisper last June?"
"Yes, it was just like this. I could not talk above a whisper."
"How long did you have trouble with your voice at that time?"
"The attack lasted about four months."
"Then what happened?"
"Then suddenly one day I was talking."
CASE 6. *Protest as hysterical stammer.* Interview:
"Fear, say the word 'fear'."
"F-f-ff-ff-f-f-f-f-f-f . . ." (*Chest heaves with effort*).
"Take it a little easier. Breathe more easily."
"F-ff-fff-f-f-f-f-ff-fr-fr-f . . ."
"Fear."
"F-ff-f-f-f-f-f-f-f-ff-ff-f-f-fff-fff-fr-ff-f . . ." (*After repeated efforts, fails to say the word.*)
"How long have you been here on our Section? How many weeks? How many days?"
"T-t-t-t-t-t-t-t-t-t- . . ." (*Shakes head from side to side*).
"Say the word if you can."
"T-t-t-t-t-t-t-t-t-t-t-*two*." (*Explosive utterance*).
"That's the idea."

Commentator. Six cases are presented illustrating within the limits of a 30-minute period, some forms of protest-symptoms encountered in the military service. Three of these cases were recorded directly during psychiatric interview, while 3 were transcribed from previously cut records to the single disc from which this case sequence is presented.

Protest symptoms are herein represented as a series of unconsciously-determined regressive behavior-patterns that appear to contradict the military environment. All symptoms in these patients appeared in the Zone of Interior, following the basic training period. They represent some of the earlier manifestations of failure in the military service.

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PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF
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UTERINE BLEEDING AND EXTRAGENITAL DISTURBANCES

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THE causes of prolonged, excessive or frequent uterine bleeding are usually classified as: (*a*) Organic pelvic diseases, (*b*) functional endocrine imbalances, (*c*) systemic disease processes, and (*d*) blood dyscrasias.[19] The last 2 groups are conceded a relatively minor rôle,[111] and receive serious study only after various hysterostyptics, local procedures and empiric organotherapy have been unavailing.

While this type of classification is practical from a therapeutic standpoint, it leads to certain etiologic misconstructions. It is now abundantly clear that the rhythm of uterine bleeding is the result of the ebb and flow of pituitary and ovarian hormones. Accentuation or prolongation of this bleeding may be associated with a pelvic lesion, yet the organic defect is not, in one sense, an adequate and independent cause for the bleeding. Despite the presence of various organic lesions, the uterus will have cyclic periods of freedom from bleeding. Moreover, benign pelvic lesions in general do not cause bleeding before the menarche nor after the menopause, and not at any time in very many women. Even if excessive bleeding is associated, it is controllable by endocrine therapy, and may be arrested by castration without removal of the lesion itself.[60]

Benign myometrial or adnexal lesions, therefore, can hardly be considered primary factors in uterine bleeding phenomena, although they may frequently increase bleeding by interference with hormonal mechanisms or pelvic dynamics. Such interference may equally well be ascribed to various systemic disturbances which have been found capable of altering the menses even though the pelvic organs remain anatomically normal. A minor pelvic abnormality may be purely incidental, and serve only as a pretext for surgery which could be avoided by proper attention to the general medical status of the woman.

It should be emphasized that endometrial lesions, benign or malignant, may produce arrhythmic bleeding analogous to wound bleeding, which is

entirely independent of the presence or absence of a functioning endocrine mechanism. Conversely, irregular bleeding is almost always due to a lesion of the genital tract epithelia, and prompt inspection and biopsy is demanded.

In the absence of a demonstrable pelvic lesion, the presence of a functional derangement of the endocrine glands is inferred. Having found evidence of a particular type of hormonal imbalance, we carry out an organotherapy that cures only in the sense that insulin cures diabetes. Although the direction of endocrine imbalance may have been demonstrated, we have been content to counterbalance it, without seeking further for its origin. If we exclude the ovarian dysfunctions of the menarche and menopause, and possibly those due to hereditary and congenital factors, there remain far too many instances that are unexplained, unless we impute to the endocrine mechanism a capriciousness that is biologically illogical. Our purposes here are to list the disturbances and diseases of the body that have been reported to be associated with uterine bleeding, and to estimate the frequency and importance of such causes.

Influence of the Central Nervous System. Hinsey has reviewed information pertaining to various neurogenital mechanisms.[50] The denervated genital tract in animals continues to carry out cyclic estrus behavior, conception, gestation and labor. After presacral neurectomy, or after accidental transection of the thoracic cord in humans, menstruation retains its cyclic nature and pregnancy is undisturbed. Transplanted endometrium continues to exhibit cyclic growth and bleeding phenomena, and the transplanted ovary continues to produce ova and secrete hormones.

Although the genital mechanism can thus to a large extent act without neuromotor guidance, experimental and clinical data indicate that the menstrual cycle may be modified by extraneous influences acting through one of several neurologic channels. Soon after the *sympathetic fibers to the uterus* are interrupted by presacral neurectomy, or transection of the spinal cord,[60] there occurs uterine engorgement and a short siege of uterine bleeding. The *denervated ovary* exhibits normal follicular development and the presence of dilated perifollicular vessels indicate that the vasodilator sympathetic fibers are unimportant.[50] However, it has been found that intraocular endometrial transplants fail in monkeys that have a thoracic cord transection, presumably because of lowered estrogen levels.[50]

If the *pituitary stalk* is severed, ovulation is impossible in the rabbit, although various types of afferent stimuli from the genital tract are not essential. Farris has recently demonstrated a transient increase in urinary gonadotropin in men and women following sex excitement.[26] *Sympathetic fibers to the pituitary* may also have some importance, since Friedgood and Pincus have shown that the rate of gonadotropic secretion is increased by faradic stimulation of these fibers in rabbits.[50]

Theobald believes that specific vegetative control over genital functions resides in a *hypothalamic center* in the paraventricularis and the supraopticus,[112] and that menstrual abnormalities in general are reactions of this center transmitted by its nervous connection to the hypophysis. Miller states that the majority of menorrhagias are psychogenic, and that the chemical disturbance is secondary to a psychic factor acting on the endocrine glands.[75]

Many authors have noted the effects of worry, fright, fatigue, nervous shock, sexual excesses and perversions. Miller reports the case of a newlywed who bled several days weekly, apparently because of fear of

coital pain, after treatment of a rigid hymen.[75] An "inconveniently" premature flow is said to occur in brides from fear or excitement.[35] Theobald relates the case of a woman physician, who, having had one child, began to bleed irregularly only during the time when her husband was home from his travels. Fear of pregnancy was found to be the cause.[112] A case of menorrhagia apparently arising to protect a patient from her desire for extramarital relationships is reported.[75]

Emotional shock is apt to produce amenorrhea. In 4 such cases arising after a bombing of London, Loeser did endometrial biopsies which Novak found to show endometrium arrested at the phase of the cycle at which the bombing occurred. Presumably there was an emotional interruption of hormone supply.[66] A shock may arrest a normal flow,[35] and continuous heavy bleeding may have a psychic origin.

Allen and Henry studied 100 cases of *personality disorders* and found somewhat characteristic menstrual alterations.[2] In hypomania the flow is more profuse and prolonged. Manic patients show irregularities and occasional amenorrhea. In mild depression no change was noted, while in intense depression there is at first an increase in amount and duration of flow, and later a hypomenorrhea or amenorrhea. Ripley and Papanicolaou noted no clear correlation between the disturbance and the type of menstrual irregularity.[93] In 221 patients with schizophrenia and affective disorders, they observed in general a prolongation of interval with a prolonged flow. In general, the worse the mental disease, the worse the ovarian function. Mosinger and Fiorentini reached similar conclusions, and were able to demonstrate hyperprolanuria in some patients.[81]

Hypnotic suggestion has been employed to delay the menstrual flow, and to cure an antecedent polymenorrhea.[35] Immersion of the feet in either *hot or cold water* may arrest the flow.[112]

Physical Agents. The effects of *light*, *temperature*, *pressure* and other physical factors on biologic reactions in general and on pituitary function in particular are well known in the laboratory animal, and are commonly encountered in women. *Change of climate* frequently delays the menstrual flow. The greatest number of menstrual irregularities occur during the *summer months*.[4] Gunn reviewed the evidence for a *lunar influence* and found it inconclusive.[43] Muller studied the influence of the *high altitude* of a resort on the Jungfraujoch and observed menstrual alterations of various types.[82] Many waitresses had to return to lower levels because of severe menorrhagia. A controlled experiment on 70 female rats showed a shortening of the estrus cycle. Muller believes the effect of altitude is largely on the pituitary gland, but he considers the possible effects of *excess ultraviolet radiation*, *decreased oxygen supply*, and the *local effects of low atmospheric pressure* on the vessels of the endometrium.

In 50 women *athletes* Nizza found that menstrual disorders occurred only with violent exercise during the flow.[86] Occupations involving *physical effort* led to menstrual irregularities in one-fourth of 2500 previously normal women.[17] Mayer has extensively reviewed the possible ill-effects of *trauma* and he describes several mechanisms. *Psychic trauma* before the mid-cycle may cause premature rupture of the follicle and thus shorten the cycle. Psychic trauma late in the cycle can cause a sudden premature flow, because of the splanchnic pooling of blood and uterine congestion. During the menses a psychic insult may arrest the flow entirely as a result of a sympathetico-adrenal reaction.[69] To this we may add Markee's observation that intraocularly transplanted endometrium will exhibit a secondary hemorrhage in monkeys frightened late in the menstrual period.[68]

Mayer further writes that *abdominal concussion* in the early cycle may also cause premature follicle rupture and advancement of the menses. Premenstrually a corpus luteum hematoma may be produced, with prolonged and excessive bleeding. During the flow itself, a blow to the lower abdomen can cause local endometrial disruption and an increase of bleeding.

Cerebral trauma, especially if a basal skull fracture is produced, may result in prolonged amenorrhea, although irregular bleeding may occur. Actual organic damage to the pituitary gland may be the result of local hemorrhage or pressure from edema, and a permanent hypopituitarism may develop. In some cases, Muller believes that the cerebral concussion has acted only as a severe psychic shock, and that the symptoms will regress spontaneously.[82] Hyperestrinism with endometrial hyperplasia and menorrhagia is said to be common after head trauma.[117]

Porcaro reports menorrhagia following exposure to *benzol*, and cites the similar effects of prolonged exposure to *carbon sulphide*, *phosphorus*, *mercury* and *lead*.[33] *Sedormid* or *quinine* may depress platelet production and thus lead to a hemorrhagic diathesis.[77] *Morphine*[112] and *alcohol* addictions lead to amenorrhea and loss of libido. *Ephedrine sulphate* intranasally leads to menorrhagia in occasional patients.[92]

Diseases of the Endocrine Glands. Of the primary endocrine disorders, those of the pituitary, the ovaries and the adrenals are most likely to lead to menstrual dysfunction, but the rôle of the other endocrines should not be ignored. *Hypothyroidism* has long been recognized as a cause of excessive uterine bleeding.[19,30,71,113,118] Gardiner-Hill and Smith[33] studied 59 cases of myxedema and found that of the 23 premenopausal cases 18 (78%) had menorrhagia; 15 patients who had had radiation castration never had any gross pelvic lesion, and unrecognized hypothyroidism may have been the actual cause for the bleeding. Waters and Williams point out that basal metabolic rate determinations are unreliable, and in their own series of menorrhagic hypothyroids the readings were from −22 to +5. The latter patient was clinically myxedematous, and tolerated a daily dose of 6 gr. of thyroid, with disappearance of the myxedema and the menorrhagia. The authors conclude that hypothyroidism can occur with a normal basal metabolic rate determination, and they advise clinical evaluation and therapeutic testing with thyroid medication in menorrhagic cases.[119] Blood cholesterol determinations may be misleading.[31] Shute believes that 81% of his series of functional bleeders were in occult hypothyroidism, curable by thyroid medication. The basal metabolic rates in this series were -6 ± 13.[105] This empiric use of small doses of thyroid is widely recommended and practiced. Novak, however, states that "in the overwhelming majority of cases of functional bleeding, no thyroid element appears to be concerned, and thyroid therapy is of no value."[87]

Hyperthyroidism frequently leads to diminution of libido, amenorrhea, menstrual irregularities and sterility, although menorrhagia can appear. In 35 patients, Schachter noted 3 cases of severe bleeding, and 24 other patients showed some menstrual irregularity.[99] Russell and Dean report diminution of flow or amenorrhea in most cases, and menorrhagia in only 3%. In severe hyperthyroidism only 27.5% of patients maintained normal cycles.[97]

The thyroid-ovarian relationship may be due to a specific or to a nonspecific action on the gonadal cells. Thyroid extract has a direct inhibitory action on the ovaries, and several investigators have shown that thyroxin causes ovarian degeneration.[64] An intermediate action on pitu-

itary cells may be present,[31] and a direct effect on the local metabolism of the endometrium is quite possible.

Parathyroid disease has been mentioned as a possible systemic cause for menorrhagia and the use of parathormone, calcium and viosterol is advocated.[19,20,21] More recent studies on the blood clotting mechanism indicate that calcium deficiencies *per se* are unlikely to result in bleeding tendencies, although the association can occur. Albright states, for example, that in steatorrhea vitamin D may be dissolved in the unabsorbed fat and hence hypocalcemia is produced. In addition, the fat-soluble vitamins A and K are also lost, and thus a hemorrhagic diathesis develops.[1] The same picture may result from daily doses of mineral oil, especially in pregnancy.[56]

Aubertin has studied 100 *diabetic women*.[6] Menstrual disorders followed the onset of diabetes, especially in patients near puberty, and in severe and maltreated cases. Insulin therapy frequently corrected the menstrual disorder, which usually was a transitory amenorrhea or a moderate menorrhagia. The possible mechanisms mentioned are: (*a*) An underlying pituitary disorder, (*b*) hereditary hypoplasia of islet and genital tissues, and (*c*) effects secondary to diabetes. Among the latter are included ovarian degeneration due to hyperglycemia (which has been produced in animals), and endometrial malfunction due to faulty glycogen deposition. Aubertin stresses the fact that menstruation is not seriously disturbed in adult diabetics, and disorders are usually corrected by proper insulin therapy.[7] Roulland, following the original work of Vogt, has used insulin non-specifically in patients with dysfunctional bleeding. He states that a short course of treatment with daily doses of 5 to 20 units will work promptly or not at all. The beneficial effect is not due to a pharmacologic or styptic action but may be the result of improved glycogen metabolism in the genital apparatus, or a directly anti-estrogenic effect.[95]

Infectious Diseases. Acute infectious diseases are recognized as potential causes, through toxic or debilitating effects on the genital apparatus or endocrine glands. Several months of menorrhagia may follow an acute attack of *mumps oöphoritis*.[10] *Malaria* is a possible cause.[9] Uterine bleeding has been interpreted as an integral part of the *typhoid fever* picture,[123] although amenorrhea is the usual change. Premenstrual *upper respiratory infections* usually delay the flow, and premenstrual *intestinal toxemia* may suppress a flow entirely.[62] Early in the cycle, intestinal toxemia may lead to premature forced rupture of a follicle. Novak states that *pneumonia* and *influenza* may cause transient bleeding, but amenorrhea is more common.[87] In acute suppurative *appendicitis*, Ledoux has noticed toxic ovarian enlargements. He believes that the common factor in all infectious processes is the presence of toxic products which are capable of destroying hormone in the circulating blood, ovarian follicle or stroma.[62]

In chronic infectious diseases, as for example *tuberculosis* and *leprosy*, amenorrhea is common.[26] Menstrual excess may be seen, presumably as the result of increased blood-vessel permeability due to "constitutional depravity."[87] While *syphilis* may cause amenorrhea, Perin reports 2 cases of syphilitic menometrorrhagia, with relief on antiluetic therapy.[89]

Allergy and the Menstrual Cycle. Allergic manifestations in general are exaggerated during ovulation, menstruation and the menopause.[39] In young women, the highest average reaction to allergens is obtained on the last day of menstruation.[116] Jahiel believes that reflux tubal menstruation

provides a preparatory intraperitoneal dose of degenerating menstrual fluid. At succeeding menses, the subsequent doses excite anaphylactic liver crises, hepatic colic, asthma and coryza.[55]

In some cases, dysmenorrhea, premenstrual tension and menstrual migraine are the expressions of allergy. Joachimovitz reports a case in which the allergic menorrhagia was aggravated by topical application of the allergen to the cervix, and the menstrual fluid contained large numbers of eosinophils.[58] Rowe has reviewed this subject and relates several cases of uterine bleeding as a result of food allergies.[96] Menstrually recurring purpura of Schönlein-Henoch type is thought to be of anaphylactoid type.[24] Minot noted eosinophilia in 2 cases of menstrual thrombocytopenia purpura and suggested a possible allergic background.[77]

Blood Dyscrasias. Failure of normal menstrual discharges to clot has given rise to the widespread impression that some agent of the normal clotting mechanism is lacking, or that an anticoagulant substance is present. Henning states that menstruation is a physiologic hemorrhagic diathesis with thrombopenia and a general tendency to bleed.[48] Glueck and Mirsky showed that menstrual blood does not contain prothrombin, thrombin or fibrinogen.[38] Lozner *et al.* later confirmed this work and pointed out that menstrual blood is like defibrinated blood in its behavior toward thrombin, prothrombin and fibrinogen. No anticoagulants are present but there is an increased fibrinolytic power.[67] The recent studies of Huggins *et al.* are in agreement, and the fibrinolytic enzyme is found to behave like trypsin.[51] These findings suggest that menstrual blood does actually clot within the uterus, the clot undergoing later autolysis and discharge in fluid form. In vigorous uterine bleeding there is no time for fibrinolysis, and clots are discharged externally.

Hence, if the mechanisms which arrest uterine bleeding involve the same processes by which rhexis in general is controlled, we may conclude that any hemorrhagic diathesis may find expression in accentuation and prolongation of the menstrual flow. This is indeed the case, and in a fair proportion of blood dyscrasias, the presenting symptom has been menorrhagia, occasionally with a fatal outcome.[32]

Secondary anemia does not in itself give rise to menorrhagia. In 19 cases, Kahn reported normal menses in 12, decrease of flow in 5 and excessive flow in 2. Of 6 cases of *pernicious anemia*, 5 had normal cycles and 1 was hypomenorrheic. *Splenic anemia* was associated with marked menorrhagia.[59]

Haden and Singleton studied 34 cases of *idiopathic hypochromic anemia* (Witts), of which only 1 was a man, and only 4 were postmenopausal women. Menorrhagia (50%) and other menstrual disorders (9%) appeared to be an intrinsic part of the symptom-complex. The authors state that the menstrual disturbance usually disappears as the blood picture returns to normal.[44] In a similar series of 40 women, Gray and Wintrobe report a 67.5% incidence of menorrhagia, which tended to persist despite cure of the anemia. In some patients, heavy bleeding appeared for the first time after the blood picture became normal.[41] Similarly, Hildebrandt reports a 40 year old amenorrheic who began to have normal menses when her "achylic chloranemia" was corrected.[49] A dietary-alimentary deficiency may give rise to this syndrome.[41] The menorrhagia is apt to be misinterpreted as the cause of the anemia.

In 108 cases of *aplastic anemia*, *leukemia* and *purpura*, Buxton found that in 10 women the primary complaint was menorrhagia, and that uterine bleeding was an important secondary symptom in many of the

other cases.[15] Others report bleeding in many leukemia cases and almost invariably in aplastic anemia patients.[59]

A diagnosis of *essential thrombocytopenic purpura* is suggested by severe uterine bleeding at the menarche, especially if there is a history of bleeding from other sites. Lowered platelet level, prolonged bleeding and clot retraction times and decreased capillary resistance (with clinical purpura or ecchymoses) confirm the diagnosis. In many cases, however, the picture is not so clear and recognition is difficult. The patient may have no abnormal bleeding in the past, and a normal menstrual history. Moreover, some patients do not show a lowered platelet level in the beginning of an acute attack[53] nor in a remission.[77] Minot reports 3 patients who at successive menstrual periods had a rapid fall of platelets to very low levels, with menstrual purpuric manifestations, followed by a rapid platelet rise and cessation of abnormal bleeding.[77] More commonly, he states, a patient has a chronic mild depression of platelet level, and bleeds only with further decrease. Sometimes excessive menstrual bleeding is practically the only symptom, and hence platelet counts should be watched in all intractable menorrhagias.[40]

The platelet count falls during the menses.[63,90] Genell showed that this decrease persists until the 11th day of the cycle when there is a sudden rise followed by a gradual recession, and a sudden drop on the 1st day of the subsequent flow. A rise in platelet count also follows parturition, abortion and various surgical procedures, the common factor being resorption of degenerating tissues.[34] Capillary permeability is increased in menstruating women. These findings may reflect an endocrine influence, the exaggeration of which could lead to thrombocytopenic purpura.[77]

Troland and Lee found that spleens removed from these patients yielded an acetone extract which depressed the platelet levels of rabbits. A platelet toxin, "thrombocytopen," may be present,[115] but platelet depression may be a non-specific, and inconstant effect of such extracts.[120] Such a toxin would account for the occasional appearance of purpura in the newborn infants of thrombocytopenic mothers, in the cases collected by Finn.[27]

Many authors report dramatic cures by splenectomy, when other measures have failed.[45,53,85,106] Mettier states that splenectomy is not always satisfactory, since it is dangerous in these patients, and a high percentage of patients have recurrence of symptoms.[72] Stephan, in 1921, demonstrated cessation of hemorrhage after spleen irradiation.[109] Others have used it in various hemorrhagic diseases and in menorrhagias of other cause.[16,21,28,57,104]

Malignant neoplasms, leukemia, septicemia, arsenic, benzene, Roentgen rays and radium may depress platelet production through bone marrow destruction.[72] *Secondary thrombocytopenia* results, possibly associated with menorrhagia. David has described a small epidemic of hemorrhagic purpura, which may be a new syndrome.[22] *Hemophilia* is cited as a cause for uterine bleeding,[9,94] but the existence of this disease in women is doubted, especially since ovarian hormones have been found to be of value in treatment of male hemophiliacs.

In an editorial review, Morhardt discusses Drukker's report of a case of *constitutional thrombopathy* (a form of *pseudohemophilia*).[79] The patient reported had 2 sisters who died of menorrhagia, and 3 other relatives who suffered uterine bleeding, as well as males who showed various bleeding phenomena. The blood findings are a prolonged bleeding time and a normal clotting time, prothrombin time and platelet count. Also men-

tioned are other family groups reported by Von Willebrand, Farber and Minot. Drukker believes that pseudohemophilia may be subdivided into (*a*) hemorrhagic thrombasthenia of Glanzmann, (*b*) congenital familial fibrinopenia, and (*c*) constitutional thrombopathy, as described above. *Idiopathic hypoprothrombinemia*[84] and *hereditary telangiectasis*[8] are rare conditions in which bleeding from various mucous membranes, including the uterine, may be encountered. In the latter condition, bleeding manifestations appear at puberty, before the inherent weakness of blood-vessel walls has led to visible telangiectases.

With associated bleeding phenomena, menorrhagic patients should have a detailed hematologic investigation. Not infrequently, menorrhagia is the isolated manifestation of a hemorrhagic diathesis, and the blood picture may be deceptive at times. Until the correct diagnosis is reached, frequent small blood transfusions will be helpful in most blood dyscrasias.

Avitaminoses. Scurvy is uncommon, and most of the reported cases are in men.[70,73] In an unusual series, Ohnell describes 16 female scorbutics in a total of 22 cases, and states that menorrhagia is to be expected in these cases.[88] King asserts that a prescorbutic state is common, and some impairment of physiologic function may be expected before external evidences of deficiency appear.[61] Scorbutic manifestations can be precipitated by infectious processes in individuals with chronic nutritional instability.[73] Evidence of latent scurvy has been found in 20% of autopsies.[124]

Mickelsen *et al.* demonstrated an increased vitamin C level in the plasma at the mid-cycle.[74] Winkler and Seebach, however, found no relationship between the stage of the cycle and the urinary output of ascorbic acid.[122]

Vitamin C has been recommended in treatment of menorrhagia[26,72,83,102] because of its favorable action in sealing off capillary walls and a favorable influence on blood clotting phenomena.[101] The endometrium, like other rapidly growing tissues, may require relatively large amounts of vitamin C. High levels have been found in the substance of the ovaries,[74] the corpus luteum,[11] the pituitary and the adrenal glands.[74,124] Vitamin C deficiency may lead to ovarian dysfunction.[36]

The significance of *vitamin K deficiency* in the etiology of menorrhagia is not clear. Andrus states that avitaminosis K of dietary origin is rare, perhaps because of intestinal synthesis. In intestinal disease, severe diarrheas and adsorption defects a latent K avitaminosis may exist and prothrombin times may be reduced to 60%.[3] Yet this is above the critical bleeding level of 20%. Heilig and Kantiengar point out that liver function is usually depressed during menstruation (by the Quick test), and hence the prothrombin level may fall temporarily.[46] This fall is especially marked in those patients whose prothrombin level is already depressed.

Clinical studies that stress the value of vitamin K are unfortunately lacking in adequate laboratory control.[78,108,114] Relief of dysmenorrhea, disappearance of menstrual clots and abbreviation of flow are reported.[42]

Large doses of vitamin K will not elevate the plasma prothrombin level above normal.[3] While there is no evidence that supererogatory amounts of vitamin K will in any way affect the blood clotting mechanism, Lichtman states that vitamin K possesses coagulant properties independent of the prothrombin mechanism, and may be beneficial in the absence of hypoprothrombinemia.[65] Andrus states that the vitamin is useless unless there is a deficiency,[3] and Cheney concludes that the use of vitamin K to control blood loss from the uterus is without proved success to date.[18]

Vitamin E deficiency may not exist in humans, yet there are suggested relationships to the uterine bleeding problem. Wheat germ oil restores the hypoplastic thyroid gland of rats to normal histologic appearance. Vitamin E has been recommended as a potent "anti-estrogen."[105]

The association of menorrhagia, among other possible manifestations of hyperestrinism, and *vitamin B deficiency*, results from the inability of the liver to conjugate and dispose of estrogens unless adequately supplied with B vitamins,[14] especially thiamin and riboflavin.[103] The Biskinds[11–14] have shown that castrate rats with implants of estrone pellets in the spleen, will remain anestrous provided B vitamin intake is adequate. When the rats are placed on a B deficient diet, the estrogen detoxifying function of the liver[54,125] is lost, estrogen escapes into the systemic circulation, and the rats go into estrus.[12] These investigators further point out that many women with clinical avitaminosis B have menorrhagia, premenstrual tension, mastalgias and other symptoms attributable to hyperestrinism. Conversely, patients presenting themselves because of this latter group of symptoms are likely to show lesions of B avitaminosis in addition. Uterine bleeding abates following the use of B complex, even when small myomata are present, and sometimes in the absence of clinical avitaminosis. The deficiency also leads to a depressed basal metabolic rate, which returns to normal on B therapy, but not on thyroid medication alone.[14]

Vitamin B factors, especially thiamin, are low in the American diet. Clinical evidence of deficiency is very common, and subclinical states are probably even more common.[107] Therefore, we are justified in suspecting the B deficiency-hyperestrinemia mechanism in many menorrhagics, and empiric treatment with B complex vitamins, in large doses, may be effective.

Ashworth and Sutton show that a vicious cycle may exist, since an exacerbation of B deficiency lesions occurs with the menstrual cycle, possibly as an estrogen effect.[5] The same authors elsewhere indicate that prolonged B vitamin deficiency may lead to anterior pituitary damage, and thereafter the B deficiency lesions will not completely regress on B vitamin therapy, unless it be supplemented with anterior pituitary extract.[110] Vitamin B deficiency has been shown to cause a decrease of thyrotropic and gonadotropic hormones in rats.

Wiles and Maurer found that *crude liver extract* is useful in some cases of uterine bleeding. This antihemorrhagic factor is present in saponified beef or hog liver fat.[121]

Visceral Disease. *Liver diseases*, in general, may lead to menorrhagia. This may be due to release of toxins from degenerating parenchyme, secondary hypoprothrombinemia, secondary thrombocytopenia, or to a loss of the estrogen-detoxifying function. Feminization of cirrhotic men (gynecomastia, fat deposition over the hips and testicular atrophy = Silvestrini-Corda syndrome[23]) is due to an accumulation of the estrogens that cannot be eliminated by a diseased liver. The hormone is largely in free form, and is thus more potent than when conjugated.[12,37] Women with liver disease probably develop hyperestrinism by this same mechanism.

The Quick test reveals a menstrual depression of liver function, especially if interval function is already low.[46] *Acute yellow atrophy* and *cirrhosis* are given as causes for menorrhagia.[9] Morlock and Hall state that in severe liver damage, the platelet count is depressed and prothrombin remains low despite therapy. Hemorrhagic phenomena are seen in 58.8% of cirrhotics and 78% of cases of splenic anemia, in which platelet counts are also reduced.[80]

Roentgen ray to the *spleen* promptly arrests uterine hemorrhage.[109] Among others who confirm the value of this treatment, Dannreuther states that he uses spleen irradiation routinely in juvenile menorrhagia of undetermined origin.[21] Stephan believed that a hyperfunction of the splenic reticulo-endothelial system results in excessive release of a fibrin ferment, and that this is the condition correctible by spleen irradiation.[109] In experiments on rabbits, Ikegami observed an initial decrease in the primordial and growing ovarian follicles, superseded by regrowth and better maturation, and hence he believes that improved ovarian function is a result of spleen irradiation.[52]

Various types of *heart disease*[9,20] especially in decompensated form, with passive pelvic congestion, may cause uterine bleeding. *Chronic nephritis* is listed, as well as *thrombosis* of various abdominal blood-vessels. Heilbronn states that *uterine apoplexy* with sudden hemorrhage is not rare in hypertensive arteriosclerotics, and he reports cases in 2 octogenarian sisters.[46] *Cachectic states* may lead to either amenorrhea or menorrhagia.[15]

Atypical Bleeding of Physiologic Origin. "*Implantation sign*" is common, and is due to an escape of blood from maternal sinusoids eroded by the embedding ovum. Sometimes it may persist several days and terminate in heavy bleeding which undermines and aborts the ovum. Rutherford has recently shown that about 60% of normal women have microscopic *ovulatory bleeding* at the mid-cycle.[98] In rare cases, the blood may be grossly visible ("ovulation sign," "little menstruation").[29,77] Polymenorrhea has been attributed to *multiple ovulation*, on rather tenuous evidence.[76]

Summary. The ultimate origin of very many cases of dysfunctional uterine bleeding is not sought out, and we have been willing to accept as causes either minor incidental pelvic lesions or endocrine imbalances, which may be merely intermediate effects. Relief following hormone therapy or curettage does not demonstrate a primary endocrinopathy nor a primary endometrial disease, since both measures are non-specifically helpful, and recurrence of menorrhagia may follow either. Thus, although empiric endocrine therapy or empiric curettage may be effective therapeutic short-cuts, they may only palliate and give a false impression of benefit during the time that a thorough diagnostic search might be under way.

Uterine bleeding has two dangerous implications: cancer and blood loss. The latter will force us to provide prompt therapy, but cancer can be insidious and cannot safely be kept waiting. A reasonable guide to the possible need for early diagnostic curettage is obtained by considering the patient's age, the duration and the type of bleeding. Metrorrhagia usually means a neoplastic lesion of the uterine epithelia. The totally irregular bleeding may originate from a totally irregular growth, and curettage-biopsy should not be deferred.

Menorrhagia, however, is almost always benign. If it occurs in the course of a systemic disease, the internist may, with reasonable safety, avoid complicating the medical problem by the gynecologic treatment of a condition that may disappear with the general illness (pelvic examination should not be omitted in any case). Tracing menorrhagia to an otherwise subclinical disturbance is a tedious and uncertain process, but on occasion it will suggest cures rather than palliatives, and may often avert unnecessary or fruitless surgical procedures. Accumulating data indicate that uterine bleeding commonly derives from systemic rather than purely local disturbances.

1811 PINE STREET.

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PEDIATRICS

UNDER THE CHARGE OF

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CONGENITAL HEMOLYTIC ANEMIA: A REVIEW OF PROGRESS

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The past few years have witnessed much clinical research on the hematology of congenital hemolytic anemia. Enough progress has been achieved in our understanding of the pathogenesis of this peculiar disorder to warrant the preparation of a Review at this time, even though none of the new information gathered can be characterized as highly sensa-

tional. The various distinctive features to this disorder will be discussed *seriatim*, with the comments on each feature extracted from those reports which have emphasized that feature in most detail.

The name of the disease has many synonyms as, for example, chronic hereditary hemolytic jaundice, familial hemolytic jaundice (or *icterus*), familial (or *hereditary*, or *congenital*) hemolytic anemia, familial acholuric jaundice, hemolytic ictero-anemia, congenital spherocytic anemia, splenomegalic icterus of Hayem, Minkowski-Chauffard disease. Exactly which designation one wishes to use is largely a matter of taste, since all have attained authoritative recognition in this or foreign countries. The name selected for use here was adopted largely because Blackfan, Diamond and Leister chose it for their new and definitive "Atlas of the Blood in Children."[5]

Criteria for Diagnosis. All suspected cases, according to Haden,[22c] ought to receive certain special clinical laboratory studies to establish the correctness of the diagnosis and to rule out other conflicting kinds of hemolytic anemia. Spherocytosis should be established by measuring the mean diameter and thickness of the red cells. Both plasma and urine should be free from hemoglobin (in this disorder, even in the most active stages, hemoglobinemia and hemoglobinuria are never present, because the red cells are being destroyed in the spleen, not in the circulation). Hemolysins must be absent from the plasma (hemolysins are occasionally demonstrable in other types of hemolytic anemia; splenectomy will not effect relief if the symptoms are due to such hemolysins). Auto-agglutination of the red cells never coëxists with spherocytosis. (In acquired hemolytic icterus the erythrocytes not infrequently exhibit this phenomenon.) The quality of the stroma in spherocytes is not defective (in some anemias, such as sickle-cell anemia and idiopathic hemolytic anemia, the stroma is abnormally weak, as evidenced by bizarre shapes or a tendency for rapid spontaneous lysis of the cells when the blood remains in a test tube outside the body). In Haden's opinion the abnormality lies in the shape of the cell. The stroma is normal, and the hemoglobin unaltered, so that the rounded cell functions as well as a biconcave disk as long as it remains in the circulation. For this reason splenectomy, though it has no influence on the spherocytosis or the increased hypertonic fragility which persist though to a lesser degree than before operation, will relieve all symptoms. The increased fragility in hypotonic salt solutions in congenital hemolytic anemia is dependent upon the spherocytosis, though the conditions are not necessarily or always parallel. Spherocytosis, at times, may be present without an increase in hypotonic fragility, seemingly due to some qualitative hardening of the stroma. Conversely there are rare cases in which the red cells have an apparently normal shape but their fragility is greatly increased. Haden justified these conclusions by his observations of 21 patients. In every instance splenectomy was followed by quick disappearance of the anemia and reticulocytosis and the content of bilirubin in the plasma returned to normal.

Dacie[10b] proposed the following criteria as essential to the making of a diagnosis in suspected cases: an anemia of hemolytic type, spherocytosis, an increased susceptibility of the red cells to hemolysis by hypotonic saline, an abnormal tendency of the blood to lysis *in vitro* on incubation at 37° C., and splenomegaly in which engorgement with blood is the outstanding feature. A history of recurrent anemia or jaundice over a period of years and a positive family history are confirmatory, though their absence does not exclude the diagnosis.

Clinical Features. *Inheritance.* Meulengracht's[34] 1921 study of 7 Stockholm families established that congenital hemolytic anemia is inherited as a dominant Mendelian character. Such anomalies are transmitted through the affected parent; with 50% of the siblings exhibiting the trait; normal members of an affected family cannot pass it on. A number of other geneologic studies since that of Meulengracht (*e. g.*, that of Debré *et al.*[14]) confirm the accuracy of this theory of the mode of transmission. Race[37] reëvaluated the manner of inheritance by examining blood specimens from 183 members of 26 families in which at least 1 member had the disease. He found the general pattern to be as demonstrated by Meulengracht, except for 2 deviations from the expected trend. The expected ratio of 1 sound to 1 abnormal offspring was not exactly met, and in occasional families the disorder seemed to have skipped a generation. As an explanation for the diminished ratio he pointed to the abnormally high miscarriage and infant mortality rates found in the jaundiced branches of these families, and suggested that there probably was a disproportionate number of positive inheritors among the dead children. He postulated also that the disorder-bearing gene exhibits a lack of full penetrance. Interestingly, in 3 families only 1 child was jaundiced, with parents and all other members having no demonstrable blood abnormality. These may have been instances belonging to the interesting minor group of "acquired" or non-inherited hemolytic anemia.

Special Manifestations in Infancy. Abt[1] reviewed the literature on the symptomatology in infancy, and described the progress of 3 cases personally observed. He found a total of 10 recorded instances in which symptoms had shown themselves by 4 months of age. The onset may either be insidious, or appear with terrifying suddenness to terminate acutely in death as with 1 of Diamond's[16] infants. When the illness is first manifested in early infancy, jaundice may be entirely absent, even though there is indisputable evidence of a considerable increase in destruction of blood. Jaundice varies strikingly from time to time and is most marked in a remission following a crisis. The enlarged spleen may extend below the umbilicus and completely fill the left flank. The liver may also show considerable enlargement. Both spleen and liver are usually firm. Cardiac murmurs, probably of "hemic" nature due to anemia, are occasionally noted.

Anemia is always one of the most striking features of the disease in young infants, and may be severe. In 1 of Abt's cases the number of red cells fell to 790,000 per c.mm., and the hemoglobin content similarly diminished. Bilirubinemia is always present: the icteric index is increased, and the indirect van den Bergh reaction is positive. The morphology and fragility of the red cells are the same as with adults, though there seems to be a greater tendency for atypical macrocytic red cells to be free in the circulation. Smears of the bone marrow obtained by sternal puncture reveal an increase in the number of nucleated red cells. In place of the normal 15%, 50% or over have been noted.

The sudden appearance of a hemolytic crisis is usually the first indication that the infant's blood is not normal. First come prodromal symptoms, such as lassitude, lack of appetite and fretfulness, followed promptly by deepened jaundice and increased anemia. The spleen enlarges and the urine becomes dark. Abdominal symptoms are not prominent. Crises are occasionally initiated by febrile attacks; all the symptoms become magnified, and the infant may be extremely prostrated. Anemia is most severe when fever accompanies the crisis. Periodicity in the occurrence

of these hemolytic crises is the rule. The interval between crises varies considerably. Urobilinuria becomes prominent, especially after a crisis. The stools are normal but occasionally dark. Acholia is never present. Hemoglobinuria is rare; it occurred with 1 of Abt's infants during a crisis.

Special Manifestations in Childhood. During childhood the disease exhibits more extreme deviations from its typical course than after maturity. This tendency has been emphasized especially by Diamond,[16] who showed clearly that congenital hemolytic anemia, once its presence in childhood has become manifest, often fails to progress in as benign a fashion as later in adult life. These variations from the usual course consist of more profound anemia, interference with proper skeletal growth, and cardiac enlargement with or without decompensation. Diamond comments that the saying, "adults with the disease are more jaundiced than sick," needs to be reversed to read: "children, and especially infants, with this condition are more sick than jaundiced." The younger the patient at the time of the first crisis of hemolysis, the more severe the disturbance tends to become. The anemia is generally more profound; the cells show much more tendency to variation in shape; the reticulocytes may rise to tremendous percentages, as in 1 case where they numbered about 90% of all the red cells; the fragility test may show beginning hemolysis with normal isotonic saline solutions. The spleen may become so enlarged as to fill the whole left side of the abdomen. Death may occur during an attack, even during the first, for the bone marrow of the young does not have as great an emergency store of red cells; a hemoclastic crisis may be quickly followed by all the symptoms of acute and fatal hemorrhage.

As the child passes through succeeding attacks of hemolysis with jaundice and anemia, his heart enlarges, his valves dilate and become insufficient, and cardiac decompensation may take place. Growth of his skeletal structures is interfered with; not only is stature small but the centers of ossification delay in appearance. The bones tend to become wider, with thinning cortex, in an effort to keep up maximum production of red cells. Some children have seemed to be mentally retarded. In unoperated cases continued hyperbilirubinemia may lead to the production of gall stones with subsequent danger from biliary obstruction. Early splenectomy for the infant or child with active symptoms of congenital hemolytic anemia is therefore strongly advisable, and may be necessary as a life-saving measure.

Gall Stones. An instance of gall stones in a 3 year old child has been reported by Gairdner.[19] The preoperative diagnosis was based upon a history of hemolytic anemia, an acute attack of obstructive jaundice, and Roentgen ray demonstration of a shadow suggestive of stone in the region of the gall bladder. On reviewing the literature he found that few cases of gall stones, cholecystitis or common duct obstruction by soft masses of bile pigment have been recorded, although with adults having the disease one of the prominent and most common difficulties is the propensity to biliary tract complications.

Bones. Bone changes are almost never seen in congenital hemolytic anemia.[45] Cooper,[6] however, after citing a few similar instances from the older literature, described a family in which 2 affected children had the mongoloid facies and the thickening and vertical striation of the skull-cap bones so often deemed characteristic of Cooley's erythroblastic anemia. He pointed out that these skull changes are occasionally seen also in that third form of chronic congenital hemolytic anemia—sickle-cell anemia. Diamond,[16] as already mentioned, had previously pointed out that in the

3 varieties of congenital hemolytic anemia there is marked thinning of the cortices of the bones of the extremities with increase of the medullary portions due to hypertrophy of the medullary substance.

Acute Crises. The crises which come on abruptly for no discoverable reason can be very serious and even lethal.[1,16,28,36] In fact, Curtis, Doan and Wiseman[8] several times with adult patients have had to resort to emergency splenectomy as a life-saving measure because of the severity of a hemolytic episode. Since one hemolytic episode is usually followed by others, McLaughlin[31] recommends a splenectomy for every patient who has experienced one such episode.

Outbreaks of hemolytic crises which break out within a family circle have been referred to by a number of authors.[12,37] Dedichek[15] reported 4 instances of acute crises in 1 family and 9 instances in a second family, each such outbreak lasting a month. Scott[39] has described how within an 18 day interval 4 affected brothers and sisters each experienced a crisis. Damashek[12] discussed 3 children in the same household—2 brothers and a cousin—who became successively ill within 10 days with crises which necessitated emergency splenectomy.

The cause of such outbreaks is shrouded in the same obscurity which conceals knowledge of the cause of any individual attack. Dedichek suspected that his cases were due to a "grippe" infection. The parents of Scott's cases were convinced that emotional sympathy played a large part with the latter 3 of the 4 children. Damashek hypothesized that the crises developed because of some alteration outside the bone marrow affected perhaps by splenic activation which in turn had been provoked by some environmental factor.

All authors agree that the only satisfactory treatment lies in splenectomy. Liver, iron and other medicaments are of no help. Following splenectomy, if the diagnosis is correct, the reticulocyte count returns to normal, and the icterus disappears, because blood destruction no longer takes place.[36] The spherocytosis persists, however.

The surgical treatment has been well discussed by McLaughlin, Sharpe and Cunningham,[32] in their careful report on 29 typical cases in 12 of which the spleen was removed successfully. For those individuals having a subclinical disturbance with few or no symptoms an operation is not recommended. The youngest patient of McLaughlin *et al.* was 5 years old, but Bell[2] operated successfully on a 15 month's old child, and Haden[22d] refers to an infant who was operated on at 4 months when weighing only 7 pounds, with complete recovery from symptoms.

Gripwall[21] described the crises of congenital hemolytic anemia as being: (1) thermic, (2) abdominal or (3) essential blood crises. Lowe[30] commented that the mechanism of the so-called thermic crises, if they exist divorced from other phenomena, is not clear. The abdominal crises seem to be associated with changes in liver function and structure and not necessarily with increased blood destruction. The essential blood crises are the hemolytic type producing severe, even fatal, anemia. As summarized by Lowe, the clinical features of an abdominal crisis include: (1) liver enlargement; (2) repeated attacks of nausea, vomiting, fever, and progressive jaundice, with upper right quadrant pain in the presence or absence of gall stones; (3) a direct van den Bergh reaction in the serum, or one changing from indirect to direct during the acute episode. The pathologic changes observed include: (1) marked enlargement of the liver (no histologic reports, however); (2) a perilobular congestion of

characteristic type; (3) some degree of parenchymal degeneration, varying from mild with recovery to severe with terminal acute yellow atrophy.

Lowe studied carefully the pigment excretion of a 15 year old affected boy during an abdominal crisis. There was a marked sudden increase of urinary urobilin; rapid increase of bilirubinemia with change of the van den Bergh from indirect, through slight to moderate, to strong direct type; enlargement and tenderness of the liver; and diminished hippuric acid synthesis as measured by the Quick intravenous test. These findings which suggested diminished liver function then rapidly cleared with no therapeutic attempts. There was no marked increase of blood destruction associated with this series of events. In the same patient, transfusions were followed by a progressive enlargement of the spleen. There then occurred a marked increase in blood destruction, with drop of red blood cells, hemoglobin, and reticulocytes. It is probable that the transfused red cells were sequestered in the spleen and rapidly destroyed, leading to a marked stercobilin excretion. Splenectomy was followed by a return to normal in the red blood cells, hemoglobin, reticulocytes, bilirubinemia, and pigment excretion. All clinical symptoms and signs disappeared.

McLaughlin[31] pointed out that the manipulations of surgical removal force out into the circulation much of the blood which fills the spleen, so that this organ at the start of the operation is larger and more engorged than when finally removed and sent to the pathologist. As a consequence there ensues temporarily a striking increase in the cellular elements of the circulating blood. In counts made of his group of cases in the day following operation the average rise for hemoglobin was about 4 gm.; for red cells, 1,100,000 per c.mm.; for white cells, some 17,000 per c.mm. Thus without resorting to external transfusions an autotransfusion takes place which contributes to the success of the operation, even when a profound anemia or a hemolytic crisis is in effect. By 48 hours after operation, however, the red cell readings fall nearly to their preoperative level, due presumably to a readjustment of the fluid balance.

Sharpe and Tollman[41] comment that the immediate and dramatic changes in the blood picture are characteristic only of the familial variety of hemolytic anemia; for they were not observed in 5 patients (adults) who were subjected to splenectomy because of refractory atypical non-spherocytic hemolytic anemia. Freund[18] experienced a similar failure in an 11 year old school girl with persistent lung infection and an "acquired" chronic hemolytic anemia.

One complication which occasionally follows splenectomy consists of the building up of a tremendous platelet level within the 1st week or 2 following operation.[36] Diamond[16] described 1 such instance in a child. The high platelet count, more than 1,000,000 per c.mm. at the end of the 1st week after operation, was associated with evidences of intravascular thrombosis, manifesting itself in abdominal pain, fever, leukocytosis and convulsions. Such "platelet crises" usually subside in a relatively short time.

Accessory Spleens. When active symptoms begin to recur some months or years after the patient has been symptom-free following a splenectomy, one should suspect that an accessory spleen or spleens is undergoing compensatory hypertrophy. For this reason accessory spleens should be searched for and removed during the primary splenectomy. With normal adults the incidence of accessory spleens as usually stated is about 10%,

but Morrison, Lederer and Fradkin[35] concluded, from a study of earlier authors' work, that they are more frequent than that in childhood and still more common during the neonatal period and early infancy. Curtis and White[9] classified accessory spleens, according to location, as (*a*) hilar, (*b*) gonadal, and (*c*) gastro-intestinal. Hypertrophy of the hemolymph tissues was demonstrable at autopsy in 1 of McLaughlin's[31] adult cases, in which a recurrence of symptoms had occurred. Freund[18] had reported a 10 year old boy with congenital hemolytic anemia whose symptoms were not relieved by splenectomy; necropsy, later, uncovered a remaining accessory spleen with highly active pulp.

Blood Changes Following Splenectomy. It has already been stated that following splenectomy, coincident with the subsiding of the hemolysis and the anemia, the spherocytosis grows less marked, the fragility test shows an approach to more normal values though not always, the reticulocytes diminish, the platelet count is increased transitorily, and the hyperactivity of the bone marrow subsides. Howell-Jolly bodies also begin to be evident; Pepper and Austin[36a] found them still persistent in an adult patient 28 years after the operation, and stressed that the finding of these bodies in an otherwise normal blood can be taken as a strong indication of the absence of the spleen.

An erythroblastic response to splenectomy is, of course, well known in Mediterranean (Cooley's) anemia, also known as thalassemia. Stransky and Regala[44] described 2 children in a Filipino family believed to have congenital hemolytic anemia, in whom splenectomy was followed by a pronounced erythroblastic response. With both children, 3 to 5% of the red cells were erythroblasts nearly 1 year after the operation, and there were still persistent anemia, jaundice, reticulocytosis and increased urobilinogen output, indicating that the hemolytic disease had not abated. There were, however, no more hemolytic crises. Because of the failure to improve after splenectomy and since neither of these children nor their affected father displayed abnormal red cell fragility curves, one suspects that the genetic disorder of this family does not fit into the chronic hereditary hemolytic anemia under discussion here.

Laboratory Features. *Examination of the Blood.* Dameshek[12a] has directed attention to the information which can be gained from the ordinarily neglected but highly useful procedure of direct microscopic observation of red cells in the moist smear. In a fresh coverslip preparation of blood mixed with an anticoagulant the various degrees of spherocytosis in the individual red cells can be readily noted, since many red cells will lie edgewise to the eye. Cells in stages preliminary to complete spherocytosis will appear cup-shaped, jug-shaped, or spheroidal with a dimple at one end. Furthermore, in the presence of spherocytosis, the rouleaux formations are short, bizarre, and hardly ever straight, because it is difficult for rounded red cells to become closely aligned to others equally rounded. Gripwall[21] had emphasized the selfsame points; he reported also that in the fresh smear the reticulocytes are easily recognized by their distinctive "hilus" shapes. There are grooves and depressions on the surfaces of the reticulocytes which shift about slowly during time spent in their observation. These cells do not partake in rouleaux formation.

Hill[24] studied the dimensions of the red cells of 7 cases of congenital hemolytic anemia over a 2 year period; 3 of the patients were children. In every case but 1 there was at least 1 occasion when definite spherocytosis occurred. Decrease in diameter of the red cells—microcytosis—was also

present, except for a 7 year old boy whose red cells were often macrocytic as well as spherocytic. No significant correlation could be established between the spherocytosis and the severity of symptoms, onset of crisis, rapidity of red cell regeneration, or benefit from splenectomy.

Gripwall[21] described a peculiar appearance of the upper zone of the red cell layer during the performance of the Westergren sedimentation test. Above the linear upper border of the main sedimenting mass of red cells there is seen a diffuse rather homogeneous "veil-like" layer of lagging red cells. On microscopic examination this layer can be demonstrated to consist almost exclusively of hilus-shaped reticulocytes. Since they do not clump into rouleaux they settle downward more slowly than do the more mature aggregating cells. Further investigations proved that this kind of "veiled" sedimentation occurs in all conditions in which the blood contains a good proportion of reticulocytes.

Quantitative Measurements of Fragility. With blood from normal children the hemolysis induced by a series of increasingly hypotonic salt solutions usually begins in saline concentrations of 0.48 to 0.44% and becomes complete in concentrations 0.38 to 0.30%. One of the most characteristic diagnostic signs of congenital hemolytic anemia is a diminution in the osmotic resistance of the red cells. Disintegration becomes manifest in the zone 0.80 to 0.50% saline (normal saline = 0.85% NaCl solution) and is usually complete by 0.50 to 0.40% saline.[36,38,50]

Cormick[7] commented that the fragility test as customarily employed fails to detect slight increases in red cell fragility and should be viewed as a qualitative procedure. She recommended the more sensitive quantitative fragility method of Simmel,[42] which had been used by Whitby and Hynes[49] with adults. This method consists of hemocytometric counting of the remaining non-hemolyzed cells after exposing red cell suspensions to a series of decreasing saline solutions for 1 hour at room temperature. With 50 normal children the average values were: in 0.60% saline, 0%; in 0.55% saline, 1%; in 0.50% saline, 14%; in 0.45% saline, 47%; in 0.40% saline, 81%; in 0.35% saline, 95%. With iron-deficiency anemias and other blood dyscrasias essentially similar curves resulted. By contrast congenital hemolytic anemia (2 cases) exhibited a dramatically evident increase in red cell fragility which persisted though less marked following splenectomy.

A very similar quantitative method was utilized by Dacie[10b] to follow more precisely the changes in fragility produced by splenectomy. In his hands the fragility curves, when classified on the basis of their shapes, fell naturally into 3 main groups—"tailed," "diagonal" and "normal." The "normal" curve rises steeply in the saline concentration zone between about 0.52 and 0.36%; the "diagonal" curves spread out in a gradual rise between 0.70 and 0.40%; the "tailed" curves overlap the "normal" for much of their course, but have traces of hemolysis in the higher concentrations of saline which form a "tail" at one end of the curve. In 11 of 12 patients on whom splenectomy was performed the red cell fragility eventually became improved, though with 7 patients having "tailed" curves the postoperative decrease in fragility was preceded by an immediately transitory increase in fragility. In 1 patient, first seen in a hemolytic crisis, the resistance to hemolysis ultimately became normal.

Rate of Autohemolysis of Red Cells. Dacie[10a] investigated the question of whether the spherocytes of familial hemolytic anemia will undergo autohemolysis *in vitro* more rapidly than will normal red cells. On storing fresh blood at 37° C., whether clotted or mixed with anticoagulating potas-

sium oxalate, he found that the spherocytes of 10 patients underwent considerable spontaneous lysis within 24 hours, whereas 20 control specimens from normal individuals showed only traces at 24 hours and variable moderate amounts (trace to ++) after 48 hours. The rate of autohemolysis of the spherocytes became reduced somewhat when they were suspended in normal saline rather than serum or plasma, though disintegration under these circumstances was still more rapid than that of control washed red cells. The author suggested that the increased rate of hemolysis was perhaps dependent upon an increased *in vivo* absorption of lysolecithin by the abnormal red cells. This latter substance is a lipoidal derivative, obtainable from plasma or serum, which inhibits rouleaux formation and thereby retards sedimentation. It can convert normal discoidal red cells into spheres, with crenated and "prickle" cells as intermediate stages, and can cause hemolytic degeneration if added in sufficient concentration.

Pathogenesis. Ignorance still clouds our understanding of the physiologic mechanisms whose disturbed functionings result in the clinical picture of congenital hemolytic jaundice. Authorities in the field concur that one of the cardinal features of the disturbance is spherocytosis, but there is conspicuous lack of agreement as to whether the abnormally spherically red cells are that way because of a primary defect in red cell formation within the bone marrow, or because of an abnormally acting hemolytic mechanism, congenital and endogenous in origin. Dacie[10b] has presented an impartial appraisal of these 2 theories. The remarks and references which follow are in part extracted from his discussion.

The red cells in this condition display other abnormalities in addition to being spheroidal in shape. They can be broken up by lysolecithin more easily than normal cells.[21,29,43] They undergo more rapid autohemolysis *in vitro* both before and after splenectomy.[10a,23,29] Transfusion into healthy recipients of blood from patients with congenital hemolytic anemia has shown that the cells have a shorter life than normal,[11,29] whereas healthy cells have a normal survival time when transfused into patients with congenital hemolytic anemia.[11]

The more spheroidal shape of the cell is generally accepted as being responsible for the main features of the clinical disease, such as increased fragility to hypotonic saline, increased blood destruction, icterus, anemia, reticulocytosis, and splenomegaly. That this abnormality of the red cells, ingrained and hereditary, is the primary source of the disturbance has been proposed by many workers.[21,22,29,46]

In support of the opposing hemolytic agent theory is the demonstration that spherocytosis and increased fragility are not necessarily congenital in origin, but can be evoked by a variety of acquired anemias and by other diseases. Dameshek and Schwartz[13] energetically champion this view. From perusal of the literature and detailed hematologic study of 4 cases of acute hemolytic anemia they concluded that: (*a*) spherocytes are formed outside of the bone marrow; (*b*) spherocytosis develops only in mature red cells; (*c*) a hemolytic agent, such as is present in hemolytic sera, is responsible for its development.

Dacie[10b] lists a number of different disorders in which spherocytosis and increased fragility have been described, among them myelosclerosis and allied syndromes, leukemia, erythroblastosis fetalis, normal fetuses *in utero*, carcinomatosis of bone, lymphadenoma, ovarian dermoid cyst, lymphosarcoma of the pancreas, pneumonia, lymphadenoma, and lymphatic leukemia. The red cell changes and congestion of the spleen can

be caused also by administration of hemolytic immune sera to experimental animals[13,36,47] and by hemolytic poisonings in man, such as those due to sulfonamides.[20,23] Significantly, spherocytosis and increased fragility can be produced only *in vivo*. None of the known hemolytic agents produce these changes when added to red cells *in vitro*.

The failure to find free hemolysin in the blood of congenital hemolytic anemia cases has been explained by Dameshek and Schwartz by the hypothesis that the hemolysin responsible (of the immune body type) does not circulate in detectable amounts but remains fixed to the red cells and other tissue cells. Singer[43b] pointed out that this theory cannot be reconciled with the fact that normal cells, transfused into patients with congenital hemolytic anemia, have a normal longevity.[11]

Josephs[25] suggested that in congenital hemolytic jaundice some substance may be lacking which in normals helps to maintain the normal equilibrium between formation and destruction of blood.

The persistence of abnormal cells after removal of the spleen demonstrates that this organ alone is not responsible for the abnormalities, though its removal reduces the rate of hemolysis to limits which can be satisfactorily compensated for.

The mechanism of hemolysis within the spleen is not clear. Erythrophagocytosis is generally inconspicuous, indicating a humoral rather than a cellular type of destruction. Some authors[17,21] have attributed hemolysis to the action of lysolecithin[3,4] produced in excessive quantities by a spleen in which an unusual degree of circulatory stasis is assumed to occur. Recent claims[21,29,43a] that the red cells in familial hemolytic anemia are unusually sensitive to the hemolytic effect of lysolecithin appear to fit in with these ideas. Ham and Castle[23] believe that circulatory stasis of a normal degree, acting upon cells which are unusually susceptible to its effects, is sufficient to account for the increased hemolysis. Whipple[48] and Dacie[10b] suggest that stagnation in the spleen may be selective; normal discoidal cells may have no difficulty in traversing the spleen, but spherocytes, possibly because of their spheroidal shape, cannot pass through the stomata of the splenic sinuses.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF OCTOBER 16, 1945

An Evaluation of the Effectiveness of Globin, Albumin, Hemoglobin and Oxypolygelatin in the Treatment of Hemorrhagic Shock.* A. S. Hamilton and W. M. Parkins (Harrison Dept. of Surgical Research, Univ. of Penna.) The efficacy of colloid solutions as plasma substitutes following hemorrhage has been tested by two procedures. These procedures were planned to produce moderate and severe degrees of circulatory deficiencies.

Thirty-five dogs under light nembutal anesthesia were bled (4 cc. per kg. per minute) to a blood pressure end-point of 20 mm. Hg and immediately infused with a volume of fluid equal to the blood volume removed. A second hemorrhage, 3 hours post-infusion, was performed at the same rate and to the same end-point as the initial hemorrhage and was followed by the infusion of erythrocytes in the replacement fluid.

The following factors were considered in evaluating the efficacy of infusion fluids: degree and variation in hemodilution, change in plasma density, restoration and maintenance of blood pressure, volume of second bleeding, and survival.

The average volume of the second hemorrhage expressed as percentage

* Work done under contract with the Office of Scientific Research and Development.

of the initial bleeding volume was as follows: saline, 48; 3.3% human globin, 43; plasma, 65; 7% hemoglobin, 73; 5% oxypolygelatin, 79; 5% albumin, 88; and autotransfused blood, 95. Rapid infusion of modified human or dog globin produced vasomotor disturbances in normal dogs and was not well tolerated by severely bled dogs.

Immediately preceding the second bleeding the average hematocrit values expressed as percentage of the control value were as follows: oxypolygelatin, 33; hemoglobin, 39; 5% albumin, 41; plasma, 44; globin, 55; and saline, 66. Hemoconcentration was evident in hemoglobin-infused animals 24 hours after hemorrhage.

Blood pressure approached normal values, and was well maintained with each of the replacement fluids. The best restoration of blood pressure was obtained with autotransfused blood.

In 22 experiments, 1 hour of hypotension at 30 mm. Hg preceded the infusion. According to the criteria used in these more severe hemorrhage shock experiments plasma consistently gave the most favorable results. Albumin (5 and 25%) and oxypolygelatin were definitely superior to saline. The concentrated albumin required about 1½ to 3 hours to produce a degree of dilution comparable to that obtained with plasma.

The Effects of Alterations in the Arterial Tensions of Carbon Dioxide and Oxygen on the Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men.* S. S. KETY and C. F. SCHMIDT (Dept. of Pharmacology, Univ. of Penna.) By means of the nitrous oxide method previously reported,[1] quantitative measurements were made of blood flow and oxygen consumption in the brains of unanesthetized healthy young men under normal basal conditions and during active and passive hyperventilation with room air, inhalation of 5 and 7% CO_2 with 21% O_2, of 85 to 100% O_2, and of 10% O_2. The average results are presented in Table 1:

TABLE 1.—CHANGES IN CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION UNDER THE VARIOUS CONDITIONS

Experimental procedure	No. subjects	Cerebral blood flow (cc./100 gm./min.) Control	Exp.	Change (%)	Cerebral O_2 consumption (cc./100 gm./min.) Control	Exp.	Change (%)
1. Active hyperventilation	7	70	47	−32	4.3	4.9	+15
2. Passive hyperventilation	5	66	41	−36	4.7	4.7	0
3. 5% CO_2 inhalation . .	6	71	112	+58	4.2	4.6	+ 9
4. 7% CO_2 inhalation . .	2	64	144	+125	4.0	3.7	− 8
5. 85–100% O_2 inhalation .	6	67	59	−12	4.1	4.1	0
6. 10% O_2 inhalation . .	3	75	111	+48	4.2	4.1	− 2

The changes in cerebral blood flow induced by both types of hyperventilation, by 5% CO_2 and by high oxygen are all statistically significant. The results reported for low oxygen are not yet significant, due to the small number of cases, but these experiments are being continued. The reported changes in cerebral oxygen consumption are not statistically significant, except for the increase associated with active hyperventilation which was a constant finding in all experiments in that group.

It is pointed out that similar conclusions concerning changes in cerebral blood flow in man during these procedures were reached previously by others[2] using the cerebral arteriovenous oxygen difference as a measure of

* Work done under contract with the Office of Scientific Research and Development.

cerebral blood flow with the unestablished assumption that cerebral oxygen consumption remained constant. Although the present data validate this assumption under these specific conditions, there is still no warranty that under other conditions the cerebral oxygen consumption would remain constant. Recently it was found[3] that under a wider range of conditions cerebral arteriovenous oxygen difference was a very poor criterion of cerebral blood flow. This would be expected since the arteriovenous oxygen difference, being a product of both blood flow and oxygen consumption, is alone a measure of neither.

From our control data it is now possible to derive a first approximation to the total cerebral blood flow and oxygen consumption of the human brain under basal conditions and the respective proportion of those to cardiac output and total oxygen consumption. These data on the basis of a brain weight of 1400 gm. are presented in Table 2. We are continuing this work with further studies on the physiology, pharmacology and pathology of the cerebral circulation in man.

TABLE 2.—CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION IN RELATION TO CARDIAC OUTPUT AND TOTAL OXYGEN INTAKE

	Cerebral blood flow		Cerebral oxygen consumption	
Subject	Cc./min.	% of cardiac output*	Cc./min.	% of total O_2 intake by body
SH	826	20.2	55	20.1
LE	925	18.2	64	24.0
MH	896	20.4	60	21.6
OM	1050	21.4	69	29.8
WH	938	20.0	62	24.4
Mean	927	20.0	62	24.0

* Cardiac output calculated from ballistocardiograms using the original formula of Starr *et al.*[4] and the correction factor 1.18 of Cournand *et al.*[5]

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Respiratory Flow Rates and the Design of Oxygen Equipment.* J. R PAPPENHEIMER, J. C. LILLY and G. A. MILLIKAN (Johnson Research Foundation, Univ. of Penna.). A knowledge of respiratory flow rate patterns under various conditions of physical activity and resistance to breathing is of basic importance in determining specifications for the manufacture of oxygen delivery systems, respiratory filters, valves and other respiratory equipment. Records were shown illustrating typical respiratory flow patterns and static and dynamic pressure-flow characteristics of certain respiratory equipment. The importance of such measurements for ensuring an adequate oxygen supply and a tolerable resistance to breathing in aviation, industrial and clinical applications was pointed out.

The Effect of Morphine Upon the Circulatory and Respiratory Responses to Tilting. J. H. DREW, R. D. DRIPPS, JR., and J. H. COMROE, JR. (Depts. of Neurosurgery and Anesthesia, Hosp. of the Univ. of Penna., Harrison

* Work done under contract with the Office of Scientific Research and Development.

Dept. of Surgical Research and the Dept. of Pharmacology, Univ. of Penna. School of Medicine). It is generally thought that morphine produces no significant change in the circulation in man. However, individuals given morphine often develop symptoms such as faintness, giddiness, or dizziness which are suggestive of some alteration in the circulation. Since these symptoms occur more frequently in the upright position, we decided to investigate the effects of morphine upon the circulation of supine and erect man. Morphine was injected intravenously in 25 supine subjects; while blood pressure did not change significantly, pulse increased an average of 27% and cardiac output per minute, as measured by the ballisto-cardiograph, increased 23%. These results indicated that morphine does alter the circulation in supine man but that compensatory mechanisms prevent any detectable change in blood pressure. The circulation was then put under a strain by tilting subjects from the horizontal to 75° feet down position for 10 to 15 minutes. Before morphine only 2 of 25 subjects (8%) fainted while after administration of morphine intramuscularly 11 of 25 (44%) fainted. When the legs and thighs of these 11 were wrapped tightly with elastic bandages, only 2 of 11 (18%) fainted upon retilting. The actual site of action of morphine upon the circulation cannot be stated definitely from these data but we believe that the effect is predominantly due to peripheral vasodilatation for the following reasons: (1) Morphine did not decrease the cardiac output and hence the fall in blood pressure could not be due to direct cardiac depression. (2) It did not depress the immediate increase in pulse rate that normally occurs upon tilting, and therefore the pressure receptors and cardio-accelerator centers were not depressed by morphine. (3) The decrease in respiration was not sufficient to decrease venous return significantly.

Certain clinical implications may be derived from these experiments. Morphine should not be used unless necessary in patients who are in the erect or sitting position, or in patients whose circulation is under other strain, such as hemorrhage or shock, unless precautions are taken to prevent pooling of blood in the extremities.

Observations were also made upon the respiratory responses to tilting. Upon tilting to the feet down position, respiratory minute volume decreased 10%, whereas upon tilting back to the horizontal, minute volume increased 28%. The unexpectedly greater change upon returning the patient back to the horizontal position was probably due to distention of pulmonary capillaries by blood previously pooled in the legs.

Respiration and circulation were measured at the moment of syncope in 11 subjects. The remarkable finding was the small respiratory increase (20%) that occurred. This together with a frequent finding of pulse slowing indicates that the usual peripheral pressure-receptor and central vasomotor regulatory mechanisms either fail to respond or are suppressed under these circumstances in unanesthetized man.

BOOK REVIEWS AND NOTICES

TEXTBOOK OF OBSTETRICS. By HENRICUS J. STANDER, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Cornell University Medical College; Obstetrician and Gynecologist-in-Chief, New York Hospital and Director of the Lying-in Hospital, New York City. Third Ed. (representing the Ninth Ed. of Williams Obstetrics, the first six of which were written by the late Dr. J. Whitridge Williams). Pp. 1277; 740 figs. New York: D. Appleton-Century, 1945. Price, $10.00.

THIS new edition contains a few less pages and illustrations than the previous edition. It has been improved by the withdrawal of certain illustrations which gave what might be described as an old fashioned atmosphere, and by the introduction of many line drawings which represent the best type of pictures for many subjects, especially the mechanism of labor.

The discussions of the various subjects are well presented and well documented. Although briefer texts may be preferred by beginning students, the reviewer is convinced that the more comprehensive texts such as the present one have greater general and ultimate value. They supply a broader background of ideas as well as facts. The present edition perpetuates the high standard of medical writing set by Williams in the first 6 editions, and is not excelled in the field of obstetrical texts printed in English. D. M.

TEXTBOOK OF BACTERIOLOGY. By EDWIN O. JORDAN, PH.D., late Professor of Bacteriology and WILLIAM BURROWS, PH.D., Associate Professor of Bacteriology, University of Chicago. Fourteenth Ed. Pp. 909; 242 ills. Philadelphia and London: Saunders, 1945. Price, $7.00.

As an extremely well-rounded source of bacteriological information, this textbook should be welcome to medical students and medical technicians principally. It makes no attempt to fill the needs of students of other branches of bacteriology. The presentation follows an orderly and logical plan. The early chapters deal with the history of bacteriology, general considerations of microörganisms, the relation of bacteria to disease in humans, followed by host-parasite relationships. The bacteriology of environment with specific discussions of water, sewage, milk, and food examinations and treatment precede chapters on antigen-antibody reactions, immunology, and allergy. Then the remaining chapters consider the pathogenic bacteria, fungi, rickettsia, and viruses. Human parasitology is given a fairly extensive treatment for a book of this size in addition.

Particular attention is drawn to biological interrelations found in the study of the various types of microörganisms. Individually the microörganisms are considered not only from their biologic characteristics, but also their accepted diagnostic procedures, their immunochemical attributes, their epidemiological considerations, the disease forms produced in man, the type of immunological response, and biological prophylaxis and treatment follow. In addition related, non-pathogenic members are considered briefly.

The chapter on fungi is well illustrated with numerous photomicrographs of the various pathogenic species to supplement the text which covers the field remarkably well. The section on antigen-antibody reactions presents the modern theories for the mechanism of precipitation in a clear, concise manner. The discussion of allergy, however, is too brief for medical students and considers only the classical concepts of hypersensitivity, avoiding the recent work on abnormal types of antibodies such as the work of Loveless on reagin. Antibiotics and sulfonamides are considered sufficiently, but only in relation to bacterial physiology and to the mechanism of chemical bacteriostasis. The

term "semi-solid media" is defined in the early sections as referring to media containing 1.5% agar and it is used in this sense throughout the book. Such usage may be confusing to the student who also learns to speak of media containing 0.5% agar as "semi-solid."

The illustrations and charts used in this book are modern and pertinent. The author has made good use of electron micrographs in instances where the increased magnification permits visualization of otherwise invisible structures. References are given as footnotes and at times seem scanty in supporting statements made in the text. In general where controversial subjects are considered, the author usually takes a definite stand and expresses an opinion. Long, tedious, often uncritical, pro and con discussions of such subjects are thus eliminated.

On the whole this textbook of bacteriology is well suited to the needs of students in the medical and public health fields and for such needs it is heartily recommended. J. F.

A TEXT-BOOK OF PHARMACOGNOSY. By GEORGE EDWARD TREASE, Lecturer on Pharmacognosy and Acting Head of the School of Pharmacy in the University College of Nottingham, England. Pp. 782; 280 figs. Fourth Ed. Baltimore: Williams & Wilkins, 1945. Price, $7.50.

THIS book doubtless is useful for the purpose stated in the introduction, *viz.*, to cover the requirements in pharmacognosy for pharmaceutical examinations in most English-speaking countries; but it would be more valuable in this country if it dealt even to a small extent with substances listed in the U.S.P. and N.F. The only U.S.P. drug mentioned is Eriodictyon; even so characteristically American a drug as Cascara carries no statement of the U.S.P. name or characteristics. Most of the substances described are obsolete as drugs, though some have importance in industry. The book would have small attraction for physicians of any country and would be inferior to American texts on pharmacognosy for its avowed purpose in the U. S. C. S.

SCIENCE IN PROGRESS. By WALTER R. MILES, and others. Foreword by LORANDE LOSS WOODRUFF. Edited by GEORGE A. BAITSELL. Fourth Series. The Society of the Sigma Xi, National Lectureships 1943 and 1944. Pp. 331; 106 ills. New Haven: Yale Univ. Press, 1945. Price, $3.00.

THIS is the fourth published collection of the inspiring Sigma Xi lectures. The roster of contributors comprises 11 distinguished workers in a variety of branches of scientific research. Of special pertinence to physicians are the discussion of psychologic aspects of military aviation, by Walter R. Miles; physical structure and biologic action of nerve cells, by Detlev W. Bronk; energy and vision, by Selig Hecht; chemical transmission of nerve impulses, by Otto Loewi; present status of the Vitamin B complex, by C. A. Elvehjem; and blood and blood derivatives, by Edwin J. Cohn. The remaining chapters, by George D. Birkhoff, Peter Debye, Henry Eyring, Isadore I. Rabi, and K. C. D. Hickman, describe subjects less closely related to medicine, yet of significance to us by furnishing a background of cultural information. I. W.

A PRIMER OF ELECTROCARDIOGRAPHY. By GEORGE BURCH, M.D., F.A.C.P., Associate Professor of Medicine, Tulane University School of Medicine, etc., and TRAVIS WINSOR, M.D., Instructor in Medicine, Tulane University School of Medicine, etc. Pp. 215, 235 ills. Phila.: Lea & Febiger, 1945. Price, $3.50.

STUDENTS of electrocardiography appear to be dividing themselves into two schools of thought so far as the fundamentals of that subject are concerned. One school, numerically far the larger at this time utilizes the Einthoven equilateral triangle hypothesis and the assumptions which underlie it as the base upon which their superstructure is erected, largely with the aid of mathematical reasoning. The other school, which does not accept certain

of Einthoven's assumptions on the ground that available evidence does not support them, is interested in attempts to demonstrate relationships between potential variations of cardiac and body surface areas by purely experimental methods. The first school has a ready explanation for almost any conceivable deflection that may be encountered in an electrocardiogram while the second is having considerable difficulty in getting its science out of the swaddling clothes stage.

This book, which is intended to acquaint the beginner in electrocardiography with the fundamentals of the subject, adheres to the doctrines of the Einthoven school and does not mention other views. The text is clearly written and the illustrations superb. The book will doubtless prove completely satisfactory to those who accept the assumptions upon which it is based. This reviewer would like to point out, however, that Einthoven's law to the effect that the algebraic sum of the deflections in Leads I and III at any instant equals that of Lead II is not proven by Kirchhoff's law about currents in a network but is the expression of a simple identity that would have to hold for the relationships among any 3 positions on any body. C. W.

CLINICAL PARASITOLOGY. By CHARLES FRANKLIN CRAIG, M.D., M.A. (HON.), F.A.C.S., F.A.C.P., Col. U. S. A. (Retired), D.S.M., Formerly Director, Army Medical School, Washington, D. C.; Emeritus Professor of Tropical Medicine in Tulane University, and ERNEST CARROLL FAUST, M.A., PH.D., Professor of Parasitology in the Department of Tropical Medicine, Tulane University; Consultant to the Secretary of War, Army Epidemiologic Board on Epidemic and Tropical Diseases; Consultant U. S. Public Health Service; Honorary Consultant, Army Medical Library. Fourth Ed. Pp. 871; 305 engravings and 4 colored plates. Phila.: Lea & Febiger, 1945. Price, $10.00.

THIS revised edition of what is universally recognized as an authoritative standard text will be welcomed by all who try to keep abreast of progress in Parasitology. The first section is a General Introduction, which contains, among other orienting material, an excellent Digest of the International Rules of Zoölogical Nomenclature. (This chapter makes the book of especial service to those interested in zoölogy and taxonomy.) There follow 4 exhaustive sections entitled "Protozoa and Protozoan Infections," "Helminth and Helminthic Infections," and "Arthropods and Human Disease." Technical procedures and references to the literature complete the presentation. Illustrative photographs and line drawings are abundant, and there are some excellent color plates on malaria recognition. As a feature of this new edition, lucid paragraphs on pathogenesis have been added to each description of disease. Such discussions of the pathologic physiology of the disturbances add greatly to one's understanding of the how and why, and thereby contribute to the usefulness of this book as a text for medical students. I. W.

A MANUAL OF THE ASPERGILLI. By CHARLES THOM, Collaborator, Northern Regional Research Laboratory, formerly Principal Mycologist, Bureau of Plant Industry, U. S. Dept. of Agriculture, Washington, D. C., and KENNETH B. RAPER, Senior Microbiologist, Fermentation Division, Northern Regional Research Laboratory, Bureau of Agricultural and Industrial Chemistry, U. S. Dept. of Agriculture, Peoria, Ill. Pp. 373; 76 figs. Baltimore: Williams & Wilkins, 1945. Price, $7.00.

To biologists, the name of Thom has been almost synonymous with Aspergilli for many years; up to the present, his book on Aspergilli, written in 1926 in collaboration with Church, has been the main source of information on the subject. In this second book, Science has been fortunate in his association with Raper, who added his knowledge of chemistry and of microbiology in general to Thom's store of other information and experience.

The Aspergilli have been covered exhaustively. Part I is devoted to generalities, covering classification, morphology, methods of laboratory examination and the most important subject of variation. Part II comprises the bulk of

the book because here the characteristics of the various aspergillotic groups, species and forms are described. Thousands of strains of Aspergilli in culture. Under each group of the Aspergilli, there appear parts devoted to morphology, chemistry and perhaps pathogenesis. Part III is particularly appreciated by physicians because, in addition to a check list of species, it supplies bibliographies, arranged both according to author and by topics. In these days when antibiotics have focussed attention on the chemistry of fungi, this topical bibliography will have special appeal; the following subjects furnish headings: The production of acids (citric, fumaric, gallic, gluconic, itatonic, kojic, oxalic), antibiotics and toxins, chemistry of mold tissue, enzyme production, fat production, pathogenicity, physiology, pigments, vitamins, alcohol, ergosterol, fluorescein, hydroxylamine, and others. This topical bibliography covers three pages.

The book does not contain a separate chapter on pathogenicity or fungous disease, such as many physicians would desire. This is understandable because, as the authors state, as a manual of the Aspergilli it need not exhaustively cover the diseases they produce. Their story is of the Aspergilli. The authors, not being physicians, direct their attention toward the fungus rather than the fungous disease. None the less, data on pathogenesis are supplied in a limited way in connection with the description of those Aspergillus groups which have any pathogenic features, *e. g.*, in the discussion of *A. fumigatus*. The section on pathogenesis in the topical index supplies an extensive bibliography.

The straightforward text makes easy reading. The pages abound with illustrations of high quality. This reviewer finds such difficulty in entering an item on the debit side of the ledger that he is forced to resort to extremes by citing the color illustrations. In some of them, the green color is overdone, but this is seldom serious enough to interfere with the message intended. The authors will be rewarded for their knowledge, skill and labor because the book will be the last word on the Aspergilli for many years to come. F. W.

A Handbook for Dissectors. By J. C. Boileau Grant, M.C., M.B., Ch.B., F.R.C.S. (Edin.), Professor of Anatomy, University of Toronto, and H. A. Cates, M.B., Associate Professor of Anatomy, University of Toronto, Toronto, Canada. Second Ed. Pp. 390; 10 figs. Baltimore: Williams & Wilkins, 1945. Price, $2.50.

This dissecting guide was originally written to be used with the senior author's text-book, "A Method of Anatomy." Now the authors deem it "desirable to let the handbook exist in its own right." Consequently, some extensive changes have been effected. Former page references to "A Method of Anatomy" have been deleted and instructions for the dissection of particular parts included. All chapters, except the one on the brain, now begin with some explanatory or descriptive matter furnishing further information about the region to be dissected. A general introductory chapter and index have been added. The text proper has been increased by some 125 pages. The figures, as in the earlier edition, show the various skin incisions to be made.

The book is an admirable, concise and thoroughly systematic *vade-mecum* for the medical student in his first exploration of the human body. It is intended, not to substitute for the larger, descriptive texts, but to promote an intelligent approach to the methodology of dissection. Although very different in many obvious respects from Cunningham's 3 volume *Manual*, the *Handbook* should serve as a really practicable alternative to the almost intolerable length of the *Manual*. From a practical standpoint, the only drawback—one inherent in all dissecting guides—is that once a specific book of this sort is adopted it can seldom be adapted. It must be used in its entirety or not at all. The present work errs in this respect less than most.

This well planned little volume, then, should fill a definite need for those seeking a complete laboratory dissecting guide. J. P.

GOVERNMENT IN PUBLIC HEALTH. By HARRY S. MUSTARD, M.D., LL.D., DeLamar Professor of Public Health Practice, Columbia University. Pp. 219. New York: The Commonwealth Fund, 1945. Price, $1.50.

THIS volume is the second study to be published under the auspices of the New York Academy of Medicine Committee on Medicine and the Changing Order. It is an excellent book. The author has fulfilled admirably the request of the Committee by giving not only a clear picture of government-supported public health organization and operation, as it now exists in this country, but also political and social evolution as related to public health and "perspectives to help chart the direction of future developments."

The book first lays the groundwork for an understanding of public health. Both the biological and the sociological factors in health and disease are discussed, the character of public health problems, the professions that participate in public health work and their education and the relation of government to public health work are briefly and wisely considered. As the author expresses his conviction that it is around the practicing physician, representing medical science, that public health programs must be built, it is clear that his book has been written for the rank and file of the medical profession.

A large part of the chapter on Federal Health Services is devoted to the fascinating story of the evolution of public health, beginning with its inception in a report on Marine Hospitals by Alexander Hamilton in 1792. The present somewhat confused status of Federal Public Health is considered, and its weakness as well as its strength and value set forth.

State and local health departments are discussed, and the handicaps under which they work in our present form of political and social organization are described. The problem of integrating public health work as conducted in the three "areas of Government," Federal, State and local, is clearly presented and analyzed.

After a discussion of the various activities of Government in a public health program, an excellent summary of trends and a consideration of certain needs concludes the book.

This small and well written volume should be widely read by public spirited people both within and without the medical profession as it gives a clear understanding of the struggles going on in this country to preserve and improve the health of all our citizens. The present shortcomings and urgent needs are emphasized and it is the sort of book that every medical student should be encouraged to read if we are to aim in our medical schools to turn out scholars and citizens to take their proper place in our present day society. G. R.

CLINICAL CASE TAKING. Guides for the Study of Patients. History Taking and Physical Examination or Semiology of Disease in the Various Systems. By GEORGE R. HERRMANN, M.D., PH.D., Professor of Medicine, University of Texas. Third Ed. Pp. 192. St. Louis: C. V. Mosby, 1945. Price, $1.75.

THIS is a small compact book of considerable interest. An introduction touches briefly on the philosophy of clinical medicine, the objectives, the principles and practise, the art and technique of case-taking. A section descriptive of various divisions of a case record is followed by detailed routine outlines for history taking and for physical examination. There is considerable emphasis on the patient's mental make-up. The "Family History" is perhaps too detailed, and to the reviewer the outline for physical examination seems less well-balanced than the other sections. There is much emphasis on habitus and constitution, whereas outlines of examination for lungs, heart and abdomen are brief and incomplete. Another criticism relates to listing as "routine" such special studies as instrumental examination of the rectum and examination of sputum, gastric contents and feces. Minor criticisms relate to lack of careful proof-reading, with frequent omission of punctuation and failure to indicate clearly distinctions between headings and subheadings.

Well over half the book is devoted to case-taking in special groups of diseases: allergic, nutritional, lung, heart, peripheral vascular, etc. Effort is

made to record in some completeness all questions and examinations required in these groups. An enormous number of signs, symptoms and tests are mentioned, and the reader's medical vocabulary is increased. In some groups of cases, however, the method used is not entirely successful. Endocrine and metabolic diseases may have much in common, but the addition of hematologic disorders to the group only makes for confusion. It takes considerable mental agility to sort out the symptoms mentioned in dealing with a particular patient. For students and less experienced physicians for whom this book is primarily designed, a simpler approach would be preferable.

The form of the book is excellent, as is the use of bold faced type for painting up examinations that form the indispensable framework in every record. However, above all, the experiences and attitudes of the author as expressed in the early pages of this little volume are profoundly worthy of emulation and cannot but be helpful to younger doctors as they develop their own physician-patient relationships. J. M.

THE PHOTOCHEMISTRY OF GASES. By WILLIAM ALBERT NOYES, JR., Professor of Chemistry, Univ. of Rochester, and PHILIP ALBERT LEIGHTON, Professor of Chemistry, Stanford Univ. American Chemical Society Monograph Series, No. 86. Pp. 475. New York: Reinhold Publishing Corp., 1941. Price, $10.00.

PHOTOCHEMISTRY is a highly specialized field, which is of growing interest from the biologic viewpoint. One need merely mention such applications as photochemical processes associated with chlorophyll, sensitization phenomena related to porphyrins, the production of vitamin D by ultraviolet irradiation of ergosterol, the functional chemistry of visual purple, and the destruction of proteins and enzymes by ultraviolet light.

Earlier volumes in this monographic series have been devoted more exclusively to the applied phases of photochemistry: "Photochemical Processes," No. 43, by G. Kistiakowsky, "Photodynamic Action and Diseases Caused by Light," No. 85, by H. E. Blum, and "The Chemical Action of Ultraviolet Rays," by C. Ellis and A. A. Wells. The present monograph by Professors W. A. Noyes and P. A. Leighton is an authoritative, though technical, exposition of the fundamental theories of photochemistry and its related subject, spectroscopy. A particularly valuable feature of the book are the appendices which list all known photochemical reactions, both simple and complex substances being included. The monograph is highly recommended to all interested in the study of photochemistry. D. D.

FACIAL AND BODY PROSTHESIS. By CARL DANE CLARK, PH.D., Associate Professor of Art as Applied to Medicine, School of Medicine, Univ. of Maryland; Captain, Sanitary Corps, Army of the United States, Department of Moulage and Prosthetics, Army Medical Museum. Pp. 200; 75 ills. St. Louis: C. V. Mosby, 1945. Price, $5.00.

THE replacement by artificial substances of tissues lost by injury or disease is of particular interest and concern during the present period of post-war reconstruction. While surgical replacement is desirable whenever possible, artificial restoration by moulage has a definite place: (1) as a temporary substitute during the course of surgical reconstruction, and (2) in cases where the mutilation is too extensive or the age of the patient or conditions of health preclude surgery. The author has brought up to date and describes in detail the materials and technique employed in replacing defects of the cranium, nose, ear, cheek, hand, etc., by artificial means. One omission noted is the making of artificial eyes of acrylic resin, the development of which is one of the outstanding contributions of the Army and Navy Dental Corps during the recent war. It is hoped that in a future edition this subject will be included.

Dr. Clark has provided a useful guide to those who wish to apply their artistic talents to this particular field. R. I.

CENTRAL AUTONOMIC REGULATIONS IN HEALTH AND DISEASE, WITH SPECIAL REFERENCE TO THE HYPOTHALAMUS. By HEYMEN R. MILLER. Pp. 430; 61 ills. New York: Grune & Stratton, 1942. Price, $5.50.

THE central integration of the relatively well established peripheral autonomic mechanisms is reviewed. It should be realized that the rôle of the hypothalamus and hypothalamo-cortical integration pathways is a most complex and controversial subject. Nevertheless, such an attempt to summarize the experimental evidence under the headings of clinically important bodily functions is worth the attention of all practising physicians. Clinical material is presented to try to correlate the experimental findings.

Of special interest are the chapters on the sleep-waking mechanism and emotions. Dr. P. Anobkin's coalescent twins serve beautifully as a test of the theories presented. It is unfortunate they did not live longer.

Dr. Miller was wise in inserting the anatomic section at the end, because many run the danger of being "floundered" by such material. Even the physiologic and clinical material is difficult to grasp at times. However, this common territory where internal medicine, neurology and research must meet is worth the closest scrutiny. J. T.

TRAUMA OF THE CENTRAL NERVOUS SYSTEM. Proceedings of the Association for Research in Nervous and Mental Diseases, December 17, and 18, 1943, Pp. 679. Baltimore: Williams & Wilkins, 1945. Price, $8.00.

THIS is the twenty-third of a series of yearly volumes in which the proceedings of the Association for Research in Nervous and Mental Disease are collected and published. The advent of the war gave impetus to many types of research, and the field of central nervous system trauma profited, as is readily seen in this collection of excellent papers by many of the outstanding men in this field.

The book may be divided into 2 separate parts: experimental and clinical. The experimental group of papers is included in the first half of the book and studies range from the mechanism and pathology of trauma to gasometric blood studies during experimental trauma. Included here is a study of the history of cranial trauma from the 17th century B.C. to 1855. The bibliography for this particular paper lists 149 references. The pathology and history of cranial trauma receives considerable attention (5 papers), and experimental methods for producing cranial trauma are discussed. One paper deals with the theory of vasoparalysis due to injury, leading to vasodilatation and hemostasis, anoxia, collection of metabolites (CO_2), further dilatation and necrosis. Another study, based on 284 cases of cranial injury, shows that 11.5% had upper brain stem damage. The author then divides these patients into those with acute and those with subacute onset of "decompensation" or failure of vital signs and points out that while those with the acute syndrome usually die, the subacute group may be saved by prompt surgery.

The clinical group of papers takes up the remainder of this volume and deal primarily with diagnosis, prognosis, and management. About 35% of this group deals with diagnosis and includes papers on general clinical methods as well as on electro-encephalography and air studies. The electro-encephalograph has now become a practical tool for the use of the neurologist and neurosurgeon, and this study throws added light on a relatively new field, particularly in the matter of determining the severity of an injury and forecasting the probable long range result. The use of air studies—either ventriculogram or pneumoencephalogram—in patients with acute head injuries may not meet with the approval of all neurosurgeons, but as outlined here, the value of the information thus gained may well outweigh the risks involved. The statement is made that untoward reactions as the result of ventriculography are no worse than those with brain tumors. But it must be remembered that the mortality of ventriculography is relatively high in the presence of brain tumor unless followed by operation. Discussions of post-traumatic sequelæ occupy approximately 50% of the clinical division of the volume and subjects range from

exhaustive psychologic examinations and their prognostic value to traumatic epilepsy and the advisability of surgery for its treatment.

Of value to everyone having to do with head injuries are 3 very practical articles dealing with the use of hypertonic solutions, infections, and general management of cranial traumatic cases. The first of these is easily and quickly read; the others are explicit and detailed in their discussions of techniques and methods. The most regrettable fact is that penicillin is not discussed in any detail.

The entire volume is an excellent source of reference material, not only for the laboratory worker, but for the clinician. The considerable space allocated to the discussion of post-traumatic states should make this book of especial interest to those who will be dealing with returning war casualties. It should be in the library of anyone having more than a casual interest in cranial trauma.

J. D.

AMERICAN PHARMACY. By twenty-two authors; editor-in-chief RUFUS A. LYMAN, M.D., Dean of the College of Pharmacy and Director of the Student Health Service, Univ. of Nebraska. Pp. 525; 197 ills. Phila.: J. B. Lippincott, 1945. Price, $8.50.

ACCORDING to the preface, "Pharmacy is standing on the brink of the dawn of a new era which will require a broader background training in the basic sciences and a longer and more intensive study in the professional subjects for those who wish to practice or become leaders in the respective fields of specialization. American Pharmacy has been planned with these developments in mind. It has been designed not as a pharmaceutical compendium, but as a textbook, a teaching tool, for the specific purpose of better teaching. It serves the practicing pharmacist as a working tool. Part I of the text deals with the fundamental principles of the basic sciences as applied to pharmaceutical processes. Part II covers the field of pharmaceutical preparations with emphasis placed upon the processes involved in their manufacture. Part III gives the basic information about products of biological origin" (vitamins, endocrines, sera, vaccines, allergens). . . . "Special care has been taken to make it of value to the physician who has had no pharmaceutical training and is seeking the best media and methods for the administration of drugs." Part I is indeed a considerable advance in the desired direction and should be valuable to the prospective or practicing pharmacist as well as the thoughtful physician. Part II would be much more useful to the physician if it dealt less with standard official pharmaceutical preparations (about which his information is already adequate for his needs), and more with the newer synthetic and natural products and the specialties of various manufacturers (about which unbiased information is not easy for him to obtain); practical hints from experienced and disinterested pharmacists as to the best methods of using the newer vehicles, detergents and active drugs would greatly increase its value to the physician. Part III is concise and interesting and contains very useful tabular summaries of U.S.P. and N.N.R. sera, vaccines and diagnostic products, but no practically useful information about the new antibiotic agents. The writing is uniformly good, the information authoritative and references are given in each chapter. The greatest value of this book to physicians should lie in its discussion of modern detergents and other vehicles for cutaneous medication, for this information now is badly scattered.

C. S.

NEW BOOKS

Essentials of Neuro-psychiatry. A Textbook of Nervous and Mental Disorders. By DAVID M. OLKON, S.B., A.M., M.D., Associate Professor of Psychiatry, College of Medicine, University of Illinois. Pp. 310; 138 ills. Phila.: Lea & Febiger, 1945. Price, $4.50.

The Osseous System. A Handbook of Roentgen Diagnosis. By VINCENT W. ARCHER, M.D., Professor of Roentgenology, University of Virginia Department of Medicine. Pp. 320; 148 figs. Chicago: Year Book Publishers, 1945.

La Silicosis Pulmonar. By DR. HUGO DOONER, Medico del Departamento de Higiene Industrial de La Direccion General de Sanidad Y del Hospital San Vicente, Ex Medico Del Mineral de Cobre de Potrerilos. Pp. 195. Santiago de Chile: Zig-Zag, 1944.

The British Encyclopædia of Medical Practice, Including Medicine, Surgery, Obstetrics, Gynæcology, and other Special Subjects. Under the General Editorship of SIR HUMPHRY ROLLESTON, Bart., G.C.V.O., K.C.B., M.D., D.Sc., F.R.C.S., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge. (A) Medical Progress, 1945. Pp. 396 and 37 pp. of Index. (B) Cumulative Supplement, 1945 (in separate board binding). Pp. 255. London: Butterworth & Co., Ltd., 1945.

THESE 2 volumes continue this useful series in the manner previously described. They are obviously not suited for a brief review.

The Medical Clinics of North America. Boston Number. Symposium on Specific Methods of Treatment. Pp. 1341. Phila.: W. B. Saunders, 1945. Price, $16.00 per year.

Endurance of Young Men. Monograph of the Society for Research in Child Development. Vol. X, Serial No. 40, No. 1. Pp. 284. Washington: National Research Council, 1945. Price, $2.50.

The Way of an Investigator. A Scientist's Experiences in Medical Research. By WALTER BRADFORD CANNON, M.D., George Higginson Professor of Physiology, Emeritus, Harvard University Medical School. Pp. 229. New York: W. W. Norton, 1945. Price, $3.00.

Experimental Catatonia. A General Reaction-Form of the Central Nervous System and Its Implications for Human Pathology. By HERMAN HOLLANE DE JONG, M.D., Associate Professor of Neuro-Psychiatry, Duke University Medical School, Durham, North Carolina. Former Director of the Neurophysiological Institute, Amsterdam University, Holland. Pp. 225. Baltimore: Williams & Wilkins, 1945. Price, $4.00.

Les Etats de Carence en Belgique Pendant L'Occupation Allemande, 1940–1944. By LUCIEN BRULL and others, Institut de Clinique et de Policlinique Medicales, Universite de Liege. Pp. 285; frequent tables and charts. Liege Editions Soledi; and Paris: Hermann & Co., Editeurs, 1945.

THIS interesting monograph on the food and nutrition problem in Belgium during the German occupation should be of interest and value for those concerned with these subjects. The 16 articles cover clinical and statistical studies of such items as hemoglobin levels, school examinations; weight; blood pressure and serum protection in Out-patient Departments; malnutrition; hunger edema; vitamin deficiencies; osteomalacia; gastro-intestinal disorders, etc. Translation into English of the Introduction and various summaries facilitate reading for those not conversant with French.

E. K.

Hidden Hunger. By ICIE G. MACY, PH.D., and HAROLD H. WILLIAMS, PH.D., Research Laboratory Children's Fund of Michigan. Pp. 286. Lancaster: Jacques Cattell, 1945. Price, $3.00.

Uranium and Atomic Power. By JACK DE MENT, Research Chemist, The Mineralogist Laboratories, and H. C. DAKE, Editor, The Mineralogist Magazine. With Appendix on the Atomic Bomb. Pp. 335. Brooklyn: Chemical Publishing Co., 1945. Price, $4.00.

What the Informed Citizen Needs to Know. Edited by BRUCE BLIVEN and A. G. MEZERIK. Pp. 377. New York: Duell, Sloan and Pearce, 1945. Price, $3.00.

Personality in Arterial Hypertension. By C. A. L. BINGER, and others. Pp. 228. New York: The American Society for Research in Psychosomatic Problems, 1945. Price, $3.00.

General and Plastic Surgery. With Emphasis on War Injuries. By J. EASTMAN SHEEHAN, M.D., Professor of Plastic Reparative Surgery, New York Polyclinic Medical School and Hospital. Pp. 345. New York: Paul B. Hoeber, 1945. Price, $6.75.

Pulmonary Edema and Inflammation. An Analysis of Processes Involved in the Formation and Removal of Pulmonary Transudates and Exudates. By CECIL K. DRINKER, M.D., D.Sc., Professor of Physiology, School of Public Health, Harvard University, Boston, Mass. The Nathalie Gray Bernard Lectures Delivered at The Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, North Carolina, in December, 1944. Pp. 106. Cambridge: Harvard University Press, 1945. Price, $2.50.

Virus as Organism. Evolutionary and Ecological Aspects of Some Human Virus Diseases. By FRANK MACFARLANE BURNET, M.D., F.R.S., Director, Walter and Eliza Hall Institute of Research in Pathology and Medicine, Melbourne, Australia. Pp. 134. Cambridge: Harvard University Press, 1945. Price, $2.00.

Hahnemann. The Adventurous Career of a Medical Rebel. By MARTIN GUMPERT. Pp. 251. New York: L. B. Fischer, 1945. Price, $3.00.

New Goals for Old Age. Edited by GEORGE LAWTON. Pp. 210. New York: Columbia University Press, 1944. Price, $2.75.

What People Are. A Study of Normal Young Men. By CLARK W. HEATH. Pp. 141. Cambridge: Harvard University Press, 1945. Price, $2.00.

Men, Mind and Power. By DAVID ABRAHAMSEN, M.D., Dept. of Psychiatry, Columbia University. Pp. 155. New York: Columbia University Press, 1945. Price, $2.00.

Rorschach's Test. II. A Variety of Personality Pictures. By SAMUEL J. BECK, PH.D., Head of Psychology Laboratory, Dept. of Neuropsychiatry, Michael, Reese Hospital, Chicago. Foreword by ROY R. GRINKER, Lt. Col., M.C. Pp. 402. New York: Grune & Stratton, 1945. Price, $5.00.

Microbes of Merit. By OTTO RAHN, Professor of Bacteriology, Cornell University. Pp. 277. Lancaster: Jacques Cattell, 1945. Price, $4.00.

In the Doctor's Office. The Art of Being a Medical Assistant. By ESTHER JANE PARSONS, Formerly Research Technician, Dept. of Biochemistry, College of Physicians and Surgeons, Columbia University; Formerly Instructor in Medical Office Procedures, Paine Hall School for Medical Assistants, New York City. Pp. 295. Phila.: J. B. Lippincott, 1945. Price, $2.00.

Structure and Function of the Human Body. By RALPH N. BAILLIF, PH.D., Assistant Prof. of Anatomy, Louisiana State University, School of Medicine, New Orleans, and DONALD L. KIMMEL, PH.D., Associate Professor of Anatomy, Temple University School of Medicine, Phila. Pp. 328. Phila.: J. B. Lippincott, 1945. Price, $3.00.

NEW EDITIONS

The Autonomic Nervous System. By ALBERT KUNTZ, PH.D., M.D., Professor of Micro-anatomy in St. Louis University School of Medicine. Third Ed. Pp. 687; 91 figs. Phila.: Lea & Febiger, 1945. Price, $8.50.

A Text-book of Neuro-anatomy. By ALBERT KUNTZ, PH.D., M.D., Professor of Micro-anatomy in St. Louis University School of Medicine. Fourth Ed. Pp. 478; 325 figs. Phila.: Lea & Febiger, 1945. Price, $6.50.

Electrotherapy and Light Therapy. With the Essentials of Hydrotherapy and Mechanotherapy. By RICHARD KOVÁCS, M.D., Professor of Physical Therapy, New York Polyclinic Medical School and Hospital; Attending Physical Therapist, Manhattan State, Harlem Valley State, Columbus and West Side Hospitals. Fifth Ed. Pp. 694; 352 ills. Phila.: Lea & Febiger, 1945. Price, $8.50.

Classic Descriptions of Disease. By RALPH H. MAJOR, M.D., with 195 Contributors, Professor of Medicine, University of Kansas School of Medicine. Pp. 679; 158 ills. Springfield, Ill.: Charles C Thomas, 1945. Price, $6.50.

Manual of Psychological Medicine. For Practitioners and Students. By A. F. TREDGOLD, M.D., F.R.S.E., Consulting Physician to University College Hospital, London. Second Ed. Pp. 308. Baltimore: Williams & Wilkins, 1945. Price, $5.00.

Familial Nonreaginic Food-allergy. By ARTHUR F. COCA, M.D., Medical Director, Lederle Laboratories. Second Ed. Pp. 191. Springfield, Ill.: Charles C Thomas, 1945. Price, $3.75.

A Textbook of Surgery. By JOHN HOMANS, M.D., Clinical Professor of Surgery, Emeritus. Compiled from Lectures and Other Writings of Members of the Surgical Department of The Harvard Medical School. With a Special Bibliographical Index. Sixth Ed. Pp. 1278; 530 figs. Springfield, Ill.: Charles C Thomas, 1945. Price, $8.00.

Physical Treatment by Movement, Manipulation and Massage. By JAMES B. MENNELL, M.A., M.D., B.C.(Cantab.), etc., Consulting Physiotherapist, St. Thomas' Hospital and late Lecturer, Massage Training School. Fifth Ed. Pp. 512; 288 ills. Phila.: Blakiston, 1945. Price, $7.00.

Gould's Medical Dictionary. Edited by C. V. BROWNLOW and Staff. Fifth Ed. Pp. 1528. Phila.: Blakiston, 1945. Price, $7.50.

This edition was first printed in 1941. The edition which we have just received was reprinted in May, 1945. The usual amount of additions and corrections have been made.

E. K.

Textbook of Medicine. By Various Authors. Edited by J. J. CONYBEARE, M.C., D.M., (OXON.), F.R.C.P., Physician to Guy's Hospital, London. Seventh Ed. Pp. 1165. Baltimore: Williams & Wilkins, 1945. Price, $8.00.

Hygiene. By J. R. CURRIE, M.A., (OXON.), M.D., LL.D., (GLAS.), D.P.H., (BIRM.), F.R.C.P., (EDIN.), Professor-Emeritus of Public Health, University of Glasgow and A. G. MEARNS, B.Sc., M.D., B.Sc. (Public Health), D.P.H., (GLAS.), F.R.S., (EDIN.), Senior Lecturer and Lecturer-Examiner in Public Health, University of Glasgow. Second Ed. Pp. 432; 89 figs. Baltimore: Williams & Wilkins, 1945. Price, $6.00.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

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